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ACCELERATED PRODUCTION OF POLIOMYELITIS

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SINCE we believe that the gastrointestinal tract, from the stomodeum down, is the prime portal of entry in poliomyelitis, we thought that a food (probably fruit) which enters the gastrointestinal tract could in some way act as a precursor or catalytic enzyme on a normal constituent of the tract and accelerate the production of poliomyelitis. Various materials, together with fruit extracts, were tested.

A toxic factor has been demonstrated in the stools and urines of patients ill with poliomyelitis,[1] a fact confirmed by Kramer and his associates.[2] The agglutinin titers of blood serum for enteric organisms were observed to be increased during convalescence from poliomyelitis.[3]

Coliform organisms isolated from the stools of patients ill with poliomyelitis, the toxins of these organisms and virulent poliomyelitis virus, when combined and injected into Macacus rhesus monkeys, accelerated the production of poliomyelitis in an experiment described by one of us (J. A. T.) in 1934.[4] Subsequent attempts to repeat this experiment were unsuccessful. It was shown, however, that combinations of the enteric organisms, their toxins and poliomyelitis virus, when injected into horses, produced a potent neutralizing antiserum.[5]

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This antiserum when harvested at the proper time neutralized not only the homologous Flexner strain of virus used as the virus antigen but several other strains we were then using, while neutralizing antiserum from horses, used as a control, obtained after injection of the homologous virus itself neutralized the homologous strain only.

It was also shown that subserosal injections of virus antigen and Escherichia coli extract, as described previously, produced poliomyelitis in monkeys more quickly than did subserosal injections of virus alone.

Rivers, Sprunt and Berry [6] gave injections of tissue extract and brain emulsions repeatedly and produced acute disseminated encephalomyelitis in monkeys. Rivers and Schwentker [7] showed that repeated injections of autolyzed brain material can produce paralysis in rabbits. Later, the same authors showed that paralysis could be produced in animals given repeated injections of extracts of rabbit brain (as many as 85 intracerebral injections). Kabat, Wolf and Bezer [8] and Morgan,[9] using Freund's technic of adjuvants, produced allergic encephalitis in monkeys. Their adjuvants were in the nature of sensitizing antigens, and Morgan commented on their allergic nature. Milzer and Byrd,[10] however, used autolyzed brain tissue as an adjuvant to shorten the incubation period and to facilitate the transfer of poliomyelitis virus to cancer-free white (CFW) mice.

Many coliform organisms found in the human gastrointestinal tract can be isolated from specimens of freshly harvested fruit. It was thought, therefore, that combinations of materials might get into the gastrointestinal tract on fruits and vegetables which ripen at the particular season of the year when epidemics are most likely to occur.[11]

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The results of our attempts to initiate and accelerate poliomyelitis in monkeys and cotton rats by feeding unwashed fruits and vegetables, voluntarily or by stomach tube, were not consistent. Blind transfers from the brains and cords of animals which died after feeding experiments were negative for the virus.[12]

Later, supernates of peach skin mash were injected intracerebrally. The material was toxic and killed animals but did not produce paralysis either in toxic or in smaller doses. At intervals after the injections, cotton rats that lived were challenged with intracerebral injections of poliomyelitis virus, and this resulted in an accelerated production of paralysis. The latter experiments were, therefore, repeated with proper controls.

METHODS AND MATERIALS

It was important to select the proper animals and materials with which to work. The Lansing strain of poliomyelitis virus was considered first, but the variability of the incubation period and the rapidity with which the animals sometimes became ill caused us to reject this strain for these experiments. The intervals between the injection of virus and the resulting paralysis were often so short that the effects of an accelerator could not be determined with absolute certainty. The same objections applied to Jungeblut's strain or to our own SK cotton rat–adapted strain. Our choice, finally, was Flexner's M.V. strain which we had adapted to cotton rats, a strain which had a more constant incubation period. To avoid the hazard of a latent neurotropic virus, the cotton rat was used instead of the mouse. This, however, does not mean that the mouse or that other strains of poliomyelitis virus could not be used. Flexner and Lansing strains were actually tried in the white mouse, but the results were inconstant.

Initially, the disease was produced in the cotton rat with virus injected by multiple routes simultaneously—intracerebrally, intranasally, intraperitoneally and subcutaneously (0.1 cc., 0.25 cc. in each nostril, 2 cc. and 1 cc. of a 10 per cent suspension, respectively). Paralysis appeared regularly after the fourth series of injections, and the strain is now in its seventieth generation. Two hundred and sixty-one animals were given injections in the manner described. Only 2 survived, 10 were eaten, 3 died on the third or fourth day of unknown causes and 246 were paralyzed in from four to twelve days (chart 1, line 1).

In the earlier experiments, up to January 1946, the incubation period was as long as nine to twelve days in 36 of the 246 paralyzed animals. We did not desire an incubation period as long as twelve days. After installation of a dry icebox, so that virus virulence could be maintained at a stationary level by storage on dry ice, more consistent results were obtained by giving the animals intracerebral injections only.

Sixty animals were given intracerebral injections of 0.1 cc. of 10 per cent suspension of Flexner M.V. virus adapted to cotton rats. This dose of virus was used in all subsequent experiments and is referred to as the "virus." None of the animals lived; 5 died within five days without paralysis; 1 died from operative

12. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Attempts to Isolate Virus from Fruit, Well Water, Chicken Cords, and Dog Stools, J. Pediat. **23**:168, 1943.

trauma; 4 were found dead, eaten, on the fourth and sixth days; 50 became paralyzed and died between the fourth and eighth days after injection (chart 1, line 2).

Paralysis never appeared before the fourth day, but all animals were paralyzed between the fourth and eighth days. Thus, there was a leeway of at least four days before control animals became paralyzed, and any contrast in acceleration would be obvious. We paid little attention to an accelerator unless the animals became paralyzed within the first twenty-four to forty-eight hours. Notwithstanding the double set of previous controls (321 animals) and because reaction to an inoculation of virus is known to be variable at times, it was thought best to have simultaneous controls for each subsequent experiment as well. For accurate results, observations had to be made day and night every three hours, or many of the animals would be found dead before paralysis could be noted.

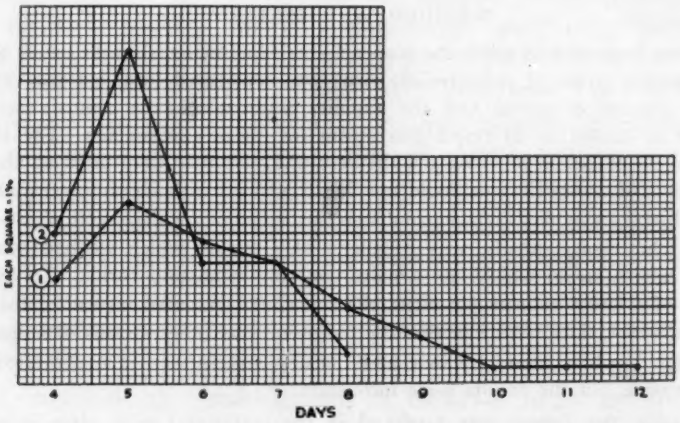

Chart 1.—Graph representing amount of paralysis produced in cotton rats with virus injected by multiple routes simultaneously. In the old series, line 1, 261 rats were given injections, of which 2 lived, 10 died of cannibalism and 3 of unknown causes; 246 were paralyzed. In the more recent series, line 2, 60 rats were given injection of virus, of which 50 rats became paralyzed, 5 died with no paralysis, 1 died of trauma and 4 died of cannibalism.

RESULTS

Many materials were tested in attempts to find an accelerator. The results obtained are summarized in tables 1 to 5.

In experiment 1, the accelerators used were, first, supernate of peach mash in varying percentages, and second, suspensions of brain and cord from rats that had died after being given injections of 10 per cent peach mash supernate. To prepare the peach supernate, washed or unwashed peach parings were weighed, ground in a Waring blender and centrifuged. The centrifuged supernate was diluted to a 10 per cent suspension in distilled water. All operations were carried out in an icebox at —10 C. This material was used in preliminary experiments to determine a nontoxic dose. To each 3 cc. of supernate and to all

subsequent fruit supernates for injection, penicillin and streptomycin solutions (containing 100 and 1,000 units of each per cubic centimeter, respectively) were routinely added in amounts of 0.03 cc. The doses given in this and all subsequent experiments were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally. In the rat cord preparation, the 10 per cent suspension of the brains and cords of animals

TABLE 1.—*Data on Experiment 1*

Sub-experiment No.	Material Injected	Original Injections *				Virus Injections		
		No. Given Injection	No. Died	No. Paralyzed	Survivors	No. Paralyzed	No. Died with Questionable Paralysis	No. Living
1	Unwashed eluted peach mash of varying percentages, from 1 to 100%, in graduated doses	12	5	0	7	6	1	0
2	Unwashed supernate of peach mash of varying percentages, from 1 to 100%, in graduated doses	10	3	0	7	6	1	0
3	Unwashed 100% (nearly) supernate of peach mash	10	9	0	1	1	0	0
4	Unwashed supernate of peach mash of varying percentages, from 5 to 100%, in graduated doses	10	2	0	8	7	1	0
5	Unwashed 100% eluate of peach mash	10	7	0	3	2	0	1
6	Washed 100% supernate of peach mash	10	1	0	9	7	1	1
7	Washed 100% eluate of peach mash	10	8	0	2	2	0	0
8	10% suspension of brain and cord of cotton rat from subexperiment 2 who died 7 days after injection	10	1	0	9	8	1	0
9	10% suspension of brain and cord of cotton rat from subexperiment 2 who died 5 days after injection	10	3	0	7	6	1	0
10	10% suspension of brain and cord of 2 cotton rats (subexperiment 9) who died 5 and 7 days after injection	10	2	0	8	6	1	1
11	Control	10	..	..	..	9	1	0

* Original injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally, given on Aug. 17, 1946. Forty-six days later, October 2, injections of virus were given to rats surviving the original injection.

that had died after injections of peach supernate was ground and lightly centrifuged, and the supernate was injected without further treatment in the same strengths and proportions as aforementioned.

In this experiment, results in 102 animals were studied. Of these, 41 died after the various injections, leaving 61 to be challenged with virus. Of the 61, only 3 survived; 7 died unobserved during the night, and it was questionable whether they had had paralysis; 51 were paralyzed (chart 2, lines 1, 2 and 3 represent experiment 1). Line 3

represents the controls which received injections in this experiment. There was acceleration, as is shown in lines 1 and 4, which represent the results in animals prepared with peach supernate. Line 2, which represents the outcome in those prepared with suspension of animal brain cord, shows some acceleration.

In the next general experiment, various injections were made prior to challenge with the virus. This series included (1) rats which had received unwashed supernate of peach skin mash obtained from skins infected with Prunus virus I (peach yellows—chart 2, line 4); (2) 5 rats previously given injection of Amoeba proteus and subsequently of the supernate of drosophila flies which had fed on peach skins and (3) 9 animals which were previously given injections of a combination of unwashed peach mash supernate and potent polio-

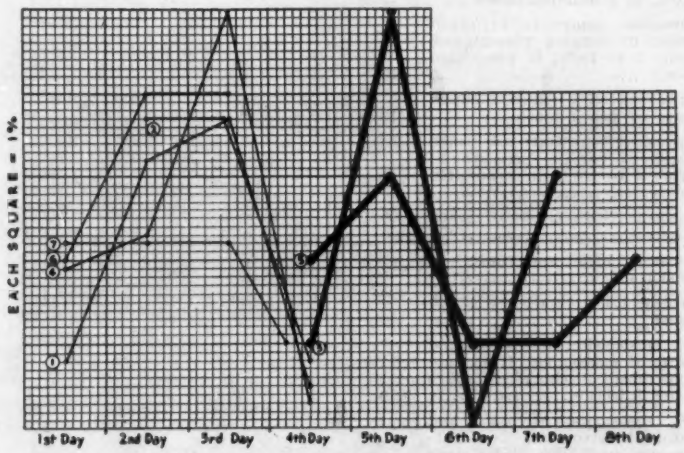

Chart 2.—Graph representing incidence of paralysis in rats in first and second experiments with accelerators. Percentage of paralysis among 37 rats given injections of peach supernate is shown in line 1; among 25 given injections of brain cord suspension in line 2, among 10 used as controls in line 3; among 26 rats given injections of peach variants in line 4; among 10 used as controls in line 5; among 5 rats given injections of a supernate of drosophila flies in line 6, and among 9 rats given injections in the neutralization experiment in line 7.

myelitis horse antiserum. The second group was too small in number for a conclusion. The last group had been given injections of multiple antigens.

The peach mash supernate in this instance was obtained from peaches infected with Prunus virus I, but the fact that they were infected made no significant difference in unpublished experiments. Again, controls were included in this series.

The fact that the 14 animals in subexperiments 4 and 5 of experiment 2 previously received injections of materials other than peach

supernate is objectionable. Therefore, no conclusions can be drawn and the data are merely recorded (table 2).

In experiment 2, of 52 animals originally given injections, 40 remained to be challenged after twenty-three days. Of these, 1 survived, 2 died with questionable paralysis and 37 had obvious paralysis after injection with the challenging virus. The animals which were given the peach supernate began to show definite paralysis within the first twenty-four hours and were all dead by the fourth day, when the controls were just starting to show symptoms of the disease. Injected

TABLE 2.—*Data on Experiment 2*

Sub-experiment No.	Material Injected	Original Injections *				Virus Injections		
		No. Given Injection	No. Died	No. Paralyzed	Survivors	No. Paralyzed	No. Died with Questionable Paralysis	No. Living
1	Unwashed supernate of peach mash — 10% concentrate of peach skins infected with virus (yellows) (Prunus virus I)....	10	1	0	9	9	0	0
2	Unwashed eluate of peach mash —100% full dose, infected with Prunus virus I.....	10	2	0	8	8	0	0
3	Unwashed supernate of peach mash obtained from noninfected peaches.....	10	1	0	9	8	1	0
4	Unwashed supernate of peach mash exposed to 100% virus from infected yellows plus an equal volume of antipoliomyelitis serum 096464.....	10	1	0	9	7	1 (chewed up)	1
5	Supernate from 1,000 drosophila flies feeding on infected peach skin	12	7	0	5	5	0	0
6	Controls	10	10	(between 4th and 8th days)			1 (trauma)	0

* Original injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally, given on Oct. 9, 1946. Twenty-three days later, November 1, injections of virus were given to rats surviving the original injection.

drosophila supernate accelerated the production of paralysis, but we could not be sure that this acceleration was due to the flies per se or to the peaches on which they were fed. The difference in results between the controls and those animals previously prepared by various injections was well defined. It was at least obvious that peach supernates injected intracerebrally were consistent accelerators.

In experiment 3, the rats had been prepared by previous injections of supernates as follows: drosophila flies grown on molasses medium, and not peach parings as in experiment 2; larvae from the preceding specimens (at least 600 larvae were harvested from the medium, ground in saline solution and centrifuged lightly, and the supernate was treated with streptomycin and penicillin as previously described); drosophila

flies grown on peach skins infected with Prunus virus I (500 drosophila flies were ground in 3 cc. of saline solution and centrifuged and the supernate treated with streptomycin and penicillin and injected); larvae from the same flies (approximately 800 larvae); "pear paring supernates" obtained from pear skins in the same manner as peach supernates; "apple mash parings" and, finally, grape skins. The usual control series was maintained.

The groups given injections of supernates of the normal drosophila flies and their larvae showed some acceleration, whereas the supernate of flies fed on peaches infected with Prunus virus I accelerated but slightly and their larvae not at all. Of 84 rats used, 8 died of trauma and 76 remained to be challenged. Of the latter, 1 survived, 15 died with questionable or no paralysis and 60 were paralyzed when challenged (chart 3, table 3).

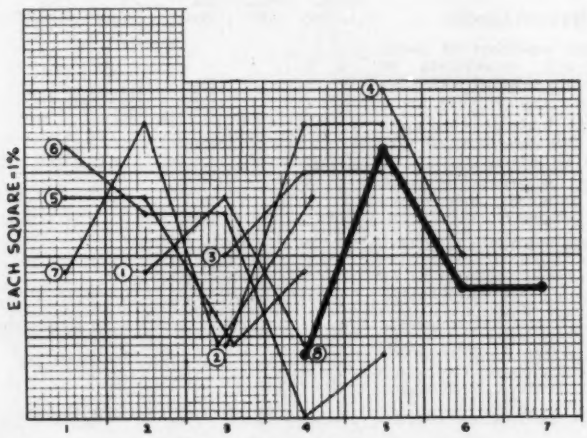

Chart 3.—Graph representing incidence of paralysis in rats in third experiment with accelerators. Percentage of paralysis among 11 rats given injections of a supernate of drosophila flies grown in molasses medium is shown in line 1; among 11 given injections of supernate of larvae of the previously mentioned drosophila flies in line 2; among 10 given injections of drosophila flies grown in virus-infected peach skin (Prunus virus I) in line 3; among 10 given the supernate of the larvae of the drosophila flies grown in the peach skins in line 4; among 11 given injections of a supernate of pear skin mash in line 5; among 12 given injections of a supernate of apple skin mash in line 6; among 11 given injections of a supernate of grape skin mash in line 7, and among 12 rats used as controls in line 8.

There was a definite acceleration in production of paralysis in all groups previously prepared with fruit supernates.

Because of the results obtained in previously reported experiments, it was decided to determine in experiment 4 whether cotton rats given injections of a peach skin supernate would show any effect when subsequently challenged with enterotoxins, a mixture of enterotoxin and enterovaccine and enterovaccine alone. Enterotoxins were prepared

by growing coliform organisms for eleven days in 0.5 per cent dextrose broth, centrifuging and filtering the supernate and adjusting it to p_H 7.3. The clear fluid remaining contained the toxin. To obtain the organisms separately from the toxin, they were grown on plain slant agar for forty-eight hours, harvested and standardized by wet weight—4 mg. to 1 cc. of the toxin. The combinations of organisms and toxins as prepared would give an enterotoxin or enterovaccine mixture.

Cotton rats were given injections of unwashed peach skin supernates from peaches infected witht Prunus virus I. Thirty days after

TABLE 3.—*Data on Experiment 3*

Sub-experiment No.	Material Injected	Original Injections *				Virus Injections		
		No. Given Injection	No. Died	No. Paralyzed	Survivors	No. Paralyzed	No. Died with Questionable Paralysis	No. Living
1	Supernate obtained from flies feeding on noninfected molasses medium—noninfected flies..	12	1	0	11	7	3	1
2	Supernate obtained from larvae feeding on noninfected molasses medium—noninfected larvae	12	1	0	11	9	2	0
3	Supernate obtained from flies feeding on infected peach skin, Prunus virus I—infected flies..	12	2	0	10	8	2	0
4	Supernate obtained from larvae feeding on virus-infected peaches, Prunus virus I—infected larvae.....	12	2	0	10	6	4	0
5	Unwashed supernate of pear skin mash—not infected.....	12	1	0	11	9	2	0
6	Unwashed supernate of apple skin mash—not infected.....	12	0	0	12	11	1	0
7	Unwashed supernate of grape skin mash—not infected.....	12	1	0	11	10	1	0
8	Controls	..	..	..	12	9	3	0

* Original injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally, given on Nov. 18, 1946. Thirty-three days later, December 21, injections of virus were given to rats surviving the original injection.

the injection, some of the animals were challenged with enterotoxin, some with combinations of enterotoxin and enterovaccine and the remainder with enterovaccine only. Thirty-three survived to be challenged. The challenging vaccine, toxin or combination produced no paralysis, although 8 animals died.

Thus, it was shown that the coliform organisms we used were not able to produce paralysis in animals, although the animals were previously given an injection of fruit supernate (table 4).

Since the cotton rat reacted as it did, an attempt was made to determine whether white rats could be made to show symptoms in similar fashion. The same percentage of peach skin supernate that had been given the cotton rats previously killed 15 to 28 white rats (table 4).

At the end of twenty-two days, 12 prepared animals and 12 controls were available. These were given injections of the virus. Two rats that died were said by one observer to have had paralysis. This was not concurred in by the other observers, and the fact, although mentioned, is discounted. Three white rats of the prepared group died at night and 7 survived. In a similar number of controls, 4 died of unknown causes and 8 survived. There was no statistical difference between the two groups, and not only were we unable to accelerate the production of poliomyelitis but we could not even adapt the virus to these animals.

Of a total of 177 animals, excluding the white rats, challenged in the 4 experiments, 147 were paralyzed, 25 died with questionable paral-

TABLE 4.—*Data on Experiment 4*

Sub-experiment No.	Material Injected	Original Injections *				Challenging Injections			
		No. Given Injections	No. Died	No. Paralyzed	Survivors	Agents	No. Paralyzed	No. Died with Questionable Paralysis	No. Living
1 (*A*) Cotton rat	Unwashed supernate of peach skin from infected peaches in 20% concentration	12	1	0	11	Enterotoxin	0	3	8
(*B*)	Same as *A*	12	1	0	11	Enterovaccine	0	1	10
(*C*)	Same as *A*	12	1	0	11	Equal volume of enterotoxin and enterovaccine	0	4	7
2 White rats †	Unwashed supernate of peach skin from infected peaches in 20% concentration	28	15	0	12	Virus injection	2	3	7
..	Control rats—12 available	..	..	..	12	Virus injection	0	4	8

* Original injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally, given on Nov. 21, 1
Thirty days later, December 21, rats in group *A* received injections of enterotoxin made by growing coliform organisms
broth and group *B* were given injections of enterovaccine made by harvesting coliform organisms grown on agar.
was standardized at 4 mg. per cubic centimeter by wet weight. All challenging doses were 0.1 cc. intracerebrally, 1 cc. sub
taneously and 2 cc. intraperitoneally.

† Original injections were given on Dec. 20, 1946. Twenty-two days later, Jan. 11, 1947, the injections of virus were giv

ysis or trauma and 5 survived. Of the 147 that were found paralyzed, 115 or 78 per cent, began to die before the controls even started to become ill. Of the 25 that had been eaten or had died during the night, 18 were dead by the third day. In all, then, 133, or 75 per cent, of the total number of challenged animals were paralyzed or dead by the third day. Thirty-two of the 147 animals became paralyzed between the fourth and sixth days. Of the 25 animals with questionable paralysis or trauma, 7 died between the fourth and seventh days. All animals were dead by the seventh day, except the 5 survivors mentioned previously (table 4).

The substances common to all fruits and vegetables are chlorophyll, succinic acid, cellulose and many other chemical entities, carbohydrates and proteins. The quantity of chlorophyll is large in the slow-growing

fruits. It was decided in experiment 5 to test chlorophyll and succinic acid as accelerators. Some delay was occasioned in finding a nonlethal dose of the chemicals.

Eventually, we discovered that succinic acid (0.03 per cent solution) could be injected, as were the materials in the earlier experiments, without killing or affecting the animal (0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally). Animals were prepared with peach supernate, succinic acid and autolyzed brain tissue (see reports of Rivers and his associates, Morgan and others), and the usual control series was included.

It is obvious from table 5 and chart 4 that succinic acid and peach supernate accelerated the production of paralysis and that the specimen of autolyzed brain and cord did not. Animals given injections of enterovaccine and later inoculated with peach supernate instead of virus

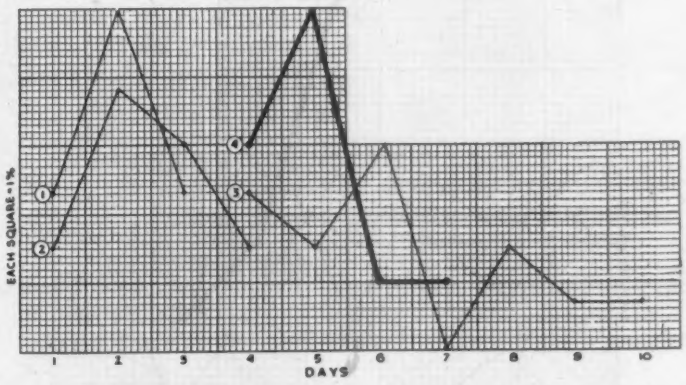

Chart 4.—Graph showing results of a portion of the fifth experiment with accelerators. Percentage of paralysis among 13 rats given injections of succinic acid is shown in line 1; among 13 given injections of peach supernate in line 2; among 13 given injections of a suspension of autolyzed brain and cord in line 3, and among 10 used as controls in line 4.

showed no paralysis (table 5, experiment 5). In this group, 5 of 14 animals died of cannibalism.

The dose of chlorophyll that would not kill or affect the rats was ascertained to be a 0.06 per cent solution given intracerebrally. Because of the presence of cyanophore glucosides in the peach, a synthetic preparation, succinonitrile, was obtained, and its nonlethal dose was found to be one of a 0.02 per cent solution intracerebrally. The usual injections of both materials (0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally) were made about two weeks before the animals were challenged with 0.1 cc. of 10 per cent saline suspension of Flexner's M.V. virus adapted to the cotton rat. At the same time, enterovaccine toxin material was injected and these rats were challenged with virus also (table 5, chart 5). It could not be said that chlorophyll

or the coliform material was a good accelerator, but it was apparent that succinonitrile and fruit supernates did accelerate the production of the disease.

The former experiments were done in 1944, 1945, 1946 and early 1947. They were repeated late in 1947.

In an experiment begun on September 13, there were 15 animals for each of four experiments, a total of 60. The first series of animals was given injections of unripened peach supernate in sterile distilled water (100 per cent suspension) as previously described. The second was given injections of the same material, in 10 per cent (10:1) suspension. The third series served as controls and received injections of sterile distilled water. The fourth series, after the usual period of observation, was given the virus only.

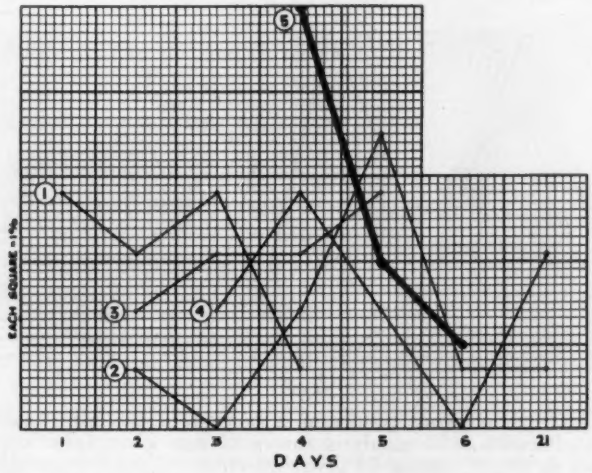

Chart 5.—Graph showing results of a portion of the fifth experiment with accelerators. Percentage of paralysis among 14 rats given injections of succinonitrile is shown in line 1; among 14 given injections of chlorophyll in line 2; among 14 given injections of a supernate of peach skin in line 3; among 14 given injections of enterovaccine in line 4 (of these 5 died of cannibalism or were found dead with no definite paralysis), and among 10 rats used as controls in line 5.

The unripened peach supernate (first series) killed the first 15 animals in two days. Two animals killed the first day in the second series of animals, which was given injections of 10 per cent (10:1) supernate, were replaced. Sterile distilled water did not kill any animals.

All the remaining animals of the second and third series, together with controls, were challenged with virus (0.1 cc. intracerebrally of the 10 per cent suspension) on Oct. 2, 1947. In the second series of the prepared animals, there were 15 deaths with paralysis within four days. In the third series, receiving sterile distilled water, there were 13 animals dead within eight days, beginning with the fifth day. One of these

animals survived, and the other died with paralysis on the tenth day. Of the control series, 1 animal was eaten up on the fourth day, and 14 animals had died with paralysis by the eighth day, beginning on

TABLE 5.—*Data on Experiment 5*

	Original Injections *					Challenging Injections										
								Day								
								1	2	3	4	5	6	7	8	9	10
								Number Paralyzed									
Material Injected	No. Given Injections and Date	Concentration	No. Died	No. Paralyzed	Survivors	Amount and Route	Agent										
Succinic acid.....	14 2/3	0.03%	1	0	13	0.1 cc. intracerebrally	10% virus suspension	3	7	3	..	..	..	..	..	..	..
Unwashed supernate from infected peaches	14 2/3	10%	1	0	13	0.1 cc. intracerebrally	10% virus suspension	2	5	4	2	..	..	..	..	..	..
Suspension of autolyzed brain and cord	14 2/10	10%	0	0	13	0.1 cc. intracerebrally	10% virus suspension	..	..	..	3†	2	4	..	2	1†	1†
Enterovaccine	14 2/3	4 mg. wet wt. per cc.	0	0	14	0.1 cc. intracerebrally	10% peach supernate	..	1†	..	2†	..	1†	1†	..	..	..
Normal passage control	..	.....	..	..	10	0.1 cc. intracerebrally	10% virus	..	..	..	3	5	1	1	..	..	..

* Original injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally, given on Feb. 3, 1947. Twenty-five days later, February 28, the challenging injection was given the survivors of the original injection.
† Found dead or died of cannibalism.

TABLE 6—*Data on Experiment 6*

	Preliminary Injections *				Challenging Injections												
						Day											
Material Injected	No. Given Injection	No. Died	No. Paralyzed	Survivors	No. Given Injection	1	2	3	4	5	6	7	8	9	10	11	21
Succinonitrile, 0.02% solution, injected 20 days before challenge	14	0	0	14	14	4 P†	3 P 2 C	4 P	1 P	....	....	..	..	..	..	..	..
Chlorophyll, 0.06% solution, injected 16 days before challenge	14	0	0	14	14	1 ?	1 P	1 C	2 P 1 C	5 P 1 ?	1 P	0	0	0	0	0	1 Living
Peach skin extract, 10% solution, injected 32 days before challenge	14	0	0	14	14	2 P	3 P 2 C	3 P	4 P	....	....	..	..	..	..	..	..
Enterovaccine, 4 mg./cc. wet weight, injected 32 days before challenge	14	0	0	14	14	0	0	2 P 1 C	4 P	2 P	1 ? 2 C	0	0	0	0	0	2 Living
Control	..	..	..	..	..	0	0	1 ?	5 P	2 P	1 P 1 ?	0	0	0	0	0	0

* Preliminary injections were 0.1 cc. intracerebrally, 1 cc. subcutaneously and 2 cc. intraperitoneally. Later, all groups received 10 per cent suspension of Flexner's M. V. virus, 0.1 cc. intracerebrally, on the same day.
† ? indicates rats which were paralyzed and C, rats which died through cannibalism.

the fifth day. Thus, it was seen that paralysis appeared more quickly in the prepared animals.

In a second experiment, 10 per cent (10: 1) supernate from ripened peaches was prepared in sterile distilled water and injected after

sixty-six days on dry ice. Two animals died on the first day and were replaced; 1 died on the eighth day and was not replaced.

All 14 of these animals showed paralysis between the second and the fourth day.

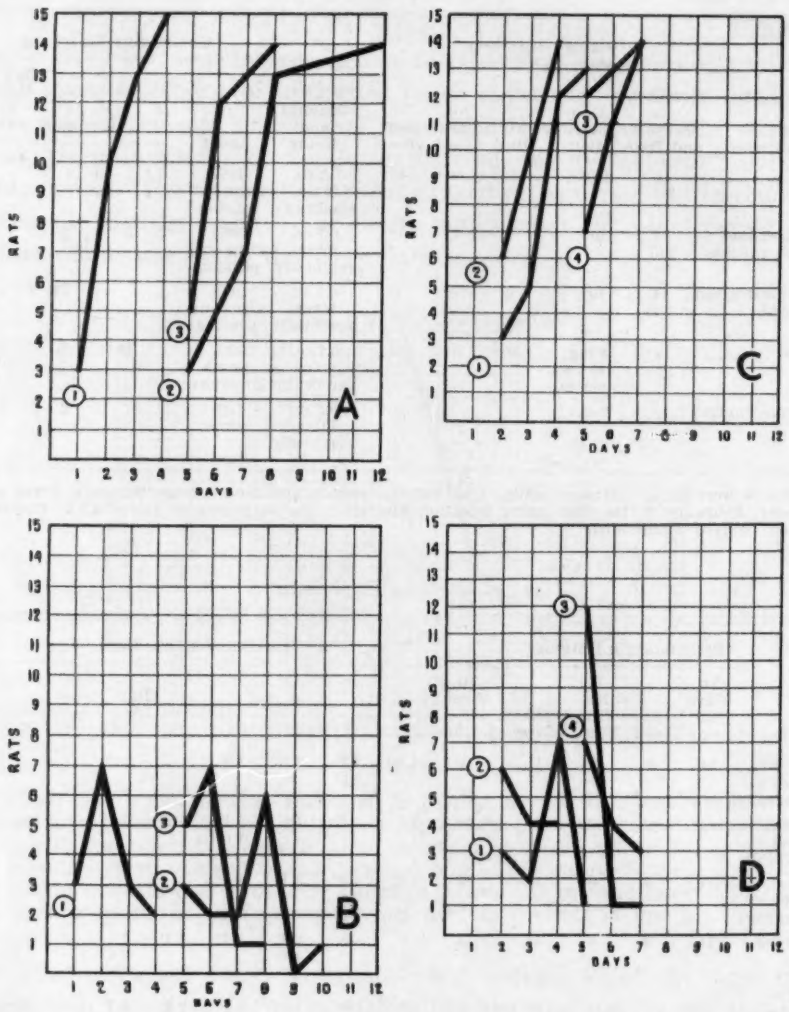

Chart 6.—Graphs showing results of challenge experiments. The lines in all graphs represent the accumulative paralysis in rats as time progressed. In graphs *A* and *B*, line 1 shows the incidence in rats given 10 per cent supernate of unripened peach; line 2, the incidence in rats given sterile distilled water, and line 3, the incidence in rats given 10 per cent virus solution as controls.

In graphs *C* and *D*, line 1 represents the incidence in rats given a 10 per cent supernate of unripened peach; line 2, the incidence in rats given a 10 per cent supernate of ripened peach; line 3, the incidence in rats given an injection of sterile distilled water, and line 4 the incidence in rats given an injection of 10 per cent solution of virus as controls. In the latter series, all materials for injection, except that given controls, was kept on dry ice for sixty-six days.

The same experiment was done with batches of 10 per cent (10: 1) suspension of unripened peaches kept sixty-six days in sterile distilled water on dry ice. Two animals died on the first day and were replaced. Fifteen animals of this group died with paralysis between the first and the fifth days after injection of virus.

A third set of animals was given injections of sterile distilled water held on dry ice for sixty-six days. One animal died the first day and was replaced. One animal died the second day of cannibalism and was replaced. Fourteen animals died with paralysis between the fifth and the seventh days.

The fourth series was a control series. Of these, 1 died, eaten up, on the second day, and 14 animals died with paralysis between the fifth and eighth days (chart 6).

Of course, it must be pointed out that the injections of fruit supernate were made in a manner that does not occur under natural circumstances.

CONCLUSION

Supernates of various fruits when injected into cotton rats conditioned them so that later injections of poliomyelitis virus that had been adapted to the cotton rat were followed by an obviously and clearly defined acceleration in the production of the experimental disease. This acceleration can also be brought about by succinic acid and succinonitrile. Suspensions of autolyzed brain tissue produced no accelerated effect.

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TRICUSPID ATRESIA

Report of Two Cases of Young Infants, with Successful Operation

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WHEN Dr. Blalock and Dr. Taussig first introduced their operation for cyanotic patients with certain types of congenital malformation of the heart, they advised [1] the postponement of the operation, whenever possible, until the patient is more than 2 years of age and its performance before puberty. It was also stated that

> . . . not only is the operation technically more difficult in infants but even if successful it is still uncertain whether the vessel anastomosed will increase sufficiently in size as the infant grows to maintain adequate circulation to the lungs.[1]

The operation introduced by Potts, Smith and Gibson [2] eliminated some of the objections raised by Blalock and Taussig, since neither the innominate nor the subclavian artery is used, and one is not, therefore, concerned with the caliber of these vessels. The youngest infant ever operated on by anyone to our knowledge was 4 months of age.[3] It was the opinion of workers until now that the risks involved in this type of operation on younger infants was too great to justify its use. As a result, many desperately ill cyanotic infants, born with serious congenital malformations of the heart, with an insufficient blood supply to the lungs, died of anoxemia before they reached the age of 4 to 6 months. We decided, therefore, to subject 2 critically ill infants to surgical intervention before what has been regarded as the optimal age for the procedure. The report of our results follows:

This study was supported by the Galter Foundation and the Mel Emerich Fund.

From the Hektoen Institute for Medical Research, the Children's Division of Cook County Hospital and the Department of Pediatrics of the University of Illinois College of Medicine.

1. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947, p. 562.

2. Potts, W. J.; Smith, S., and Gibson, S.: Anastomosis of Aorta to Pulmonary Artery, J. A. M. A. **132**:627-632 (Nov. 16) 1946.

3. Potts, W. J.: Personal communication to the authors.

REPORT OF CASES

CASE 1.—S. C., a 3 month old white male infant, was admitted to the cardiac service of the Cook County Children's Hospital on April 23, 1948, with the presenting complaint of cyanosis since the third day of life. He was born on Dec. 28, 1947 at Effingham, Ill. The delivery was normal, and the weight at birth was 5 pounds 3 ounces (2,353 Gm.). The baby was discharged from the hospital on the third postnatal day. When the child first returned home, the parents noticed that he had some blueness of his face, scalp and extremities, and this cyanosis became more prominent, gradually extending over his entire body. On Feb. 18, 1948, the baby had a severe episode of cyanosis with serious dyspnea, and a local physician advised hospitalization. During hospitalization, the infant had three severe episodes of rapid respirations, coughing, extreme cyanosis and some loss of consciousness. Oxygen was administered on these occasions. The cyanosis, however, became more pronounced, and the infant was transferred to the pediatric service of the Research and Educational Hospitals of the University of Illinois on April 1, when the examination by one of us revealed the following facts.

The infant was a 3 month old white boy in distress, crying and gasping for breath, with intense cyanosis of hands, feet, lips and mucous membranes. Respirations were 60 per minute, with some suprasternal retraction. The pulse rate was 160 and regular, and blood pressure was 76 systolic and 40 diastolic. The femoral pulse was present. The cyanosis was present even while the infant was in an oxygen tent.

The important observations were limited to the heart. The apex beat was in the fifth interspace, just outside the midclavicular line. There was a harsh systolic murmur, best heard in the second left interspace. The liver was palpable about 2 fingerbreadths below the costal line. There was no pulsation of the liver.

The fluoroscopic examination in the anteroposterior view revealed a cardiothoracic ratio of 55 per cent. The base of the heart was decidedly narrowed. There was a prominent concavity in the region of the pulmonary conus with absent pulmonary pulsations. The pulmonary fields were unusually clear. In the left oblique view, the left ventricle was definitely enlarged, and the inflow tract of this ventricle did not clear the spine until the patient was in a lateral position. The right ventricle was hypoplastic and was unusually distant from the anterior wall of the chest. The pulmonary window was wide and clear. In the right oblique view one saw the concavity of the pulmonary conus. Roentgenograms of the chest in the posteroanterior, and right and left oblique views confirmed the aforementioned fluoroscopic findings, and the esophagram revealed a normal left aortic arch.

The electrocardiogram (fig. 3) showed a definite left axis deviation, with a deep S wave in lead III and CF_2 and an R wave in leads I and II. There was slurring and notching of the QRS complexes, especially in lead II, with a wide and notched P wave in lead I. (The electrocardiographic findings were checked by Dr. A. L. Bohning.)

The examination of the blood showed a hemoglobin concentration of 15 Gm., 7,970,000 red blood cells and 10,650 leukocytes, while the differential count was 43 per cent neutrophils, 1 per cent eosinophils, 55 per cent lymphocytes and 1 per cent monocytes. The color index was 0.60.

Based on these findings, a diagnosis of tricuspid atresia with pulmonary stenosis was made and the patient transferred to the cardiac service of the

Children's Division of the Cook County Hospital for further examination and possible surgical treatment.

The circulation time was determined by the fluorescein method and was considerably shortened (three seconds).

The dextroangiocardiogram, taken within one to two seconds after administration of the iodopyracet injection (diodrast®) was started, showed incomplete

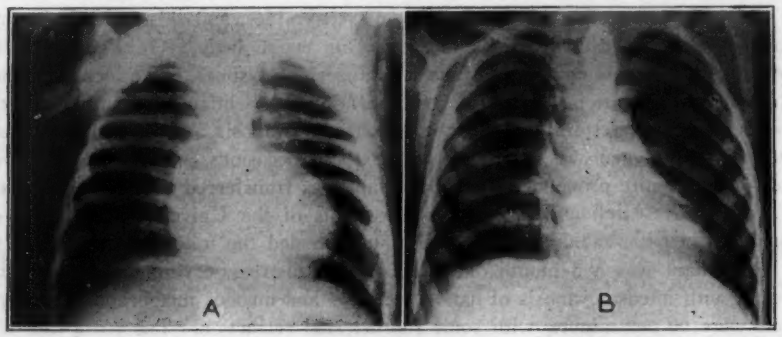

Fig. 1 (case 1).—Roentgenograms, anteroposterior view, showing (*A*) prominent concavity of pulmonary conus, clear pulmonary fields and narrow cardiac base and (*B*), normal deviation of esophagus.

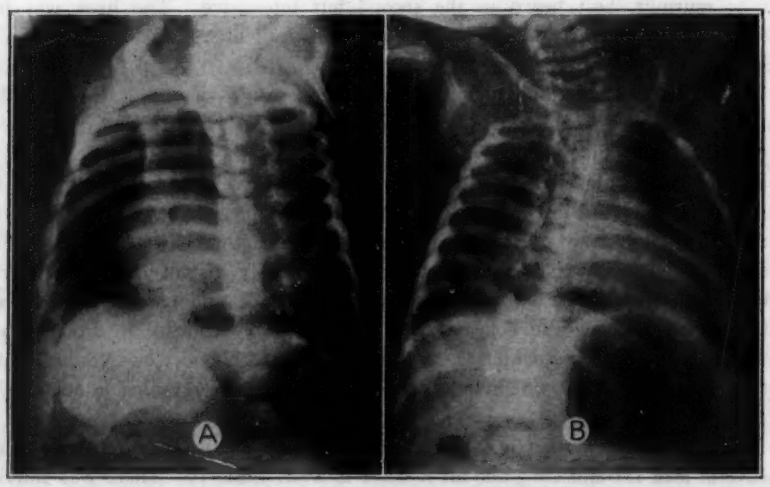

Fig. 2 (case 1).—*A* is the left oblique view showing large inflow tract of left ventricle, hypoplastic right ventricle and clear pulmonary window. *B* is the right oblique view showing concavity of pulmonary conus.

filling of the right ventricle, no pulmonary artery and filling of the region of the left auricle and of a large part of the left ventricle.

A diagnosis of tricuspid atresia with an interauricular septal defect and pulmonary stenosis, with either a patent ductus arteriosus or an interventricular septal defect, was made.

From April 23 to July 2, the infant had many episodes of severe cyanosis and extreme air hunger. Continuous oxygen was given, and during cyanotic attacks stimulants, such as epinephrine and caffeine and sodium benzoate, were necessary. The infant took his feedings poorly and weighed only 8 pounds 11 ounces (3,941 Gm.) on the day of operation, a gain of but 8 ounces (227 Gm.) during this period. It was frequently necessary to administer fluids subcutaneously because of the poor state of hydration. He was given penicillin prophylactically for almost his entire stay in the hospital.

The operation was performed on July 2. The immediate preoperative preparation consisted of improving the patient's hydration the night before surgical treatment by giving 1,000 cc. of fluids orally until 2 a.m. of the day of operation.

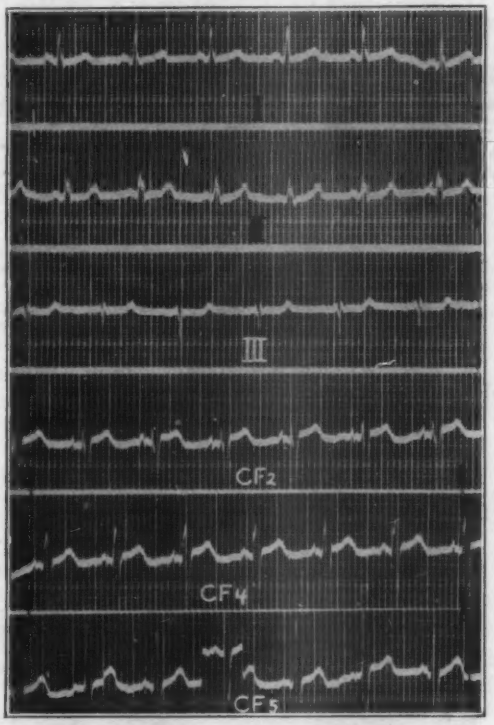

Fig. 3 (case 1).—Electrocardiogram with chest leads, showing left axis deviation.

The preoperative medication consisted of 1/500 grain (0.120 mg.) of atropine U. S. P. The anesthesia used was cyclopropane and oxygen and it was started at 8:10 a. m. and stopped at 11:40 a. m. The chest was opened through the fourth interspace. A large auricle, a large left ventricle and a small quill-sized pulmonary artery without any pulsations were observed. There was no thrill present over the pulmonary artery. The pulmonary artery and aorta were anastomosed by the procedure of Potts, Smith and Gibson. The anastomosis was 4 mm. in length. Five intercostal vessels were ligated. A good thrill was present following completion of surgical treatment. The wound was closed in layers with surgical gut U. S. P. for the subcutaneous tissues and surgical silk for the skin. Drainage was established with a catheter connected to the water seal system.

The patient withstood the operation quite well. It was noted that the cyanosis was lessened when the patient was under the anesthesia. On his return to the ward, he was placed in an oxygen tent. There was a definite machinery type murmur audible just below the left clavicle. He received 100 cc. of isotonic

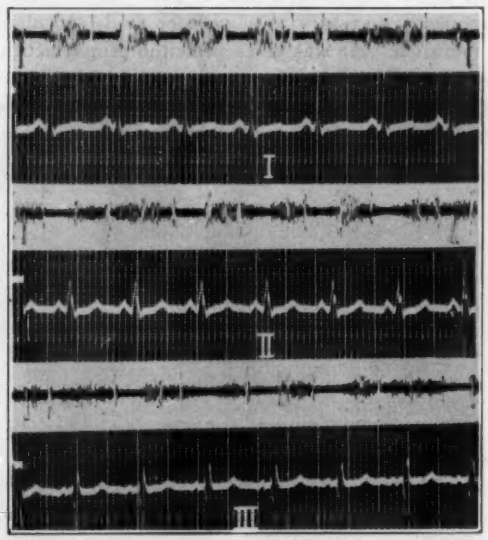

Fig. 4 (case 1).—Electrocardiogram-stethogram made after operation showing a systolic-diastolic murmur over the precordium.

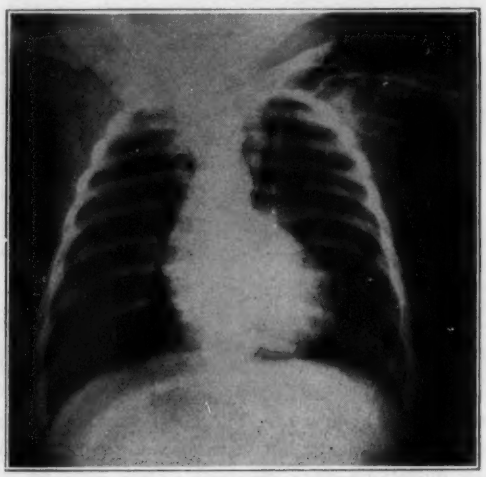

Fig. 5 (case 1).—Dextroangiocardiogram showing incomplete filling of right ventricle and filling of area of left auricle and most of left ventricle.

sodium chloride solution and 150 cc. of plasma during the operation, and was given 250 cc. of 5 per cent dextrose solution in the next twelve hours, for a total of 500 cc. in twenty-four hours. The blood pressure was taken every hour

until it stabilized at 80 systolic and 40 diastolic and was recorded every four hours thereafter. The infant responded quite well and seemed hungry, so thirty hours after the operation he was started on small amounts of water by mouth. Since he tolerated this quite well, forty-eight hours after the operation he was given a dilute formula, which was gradually concentrated.

On the second postoperative day, examination with a portable x-ray showed no evidence of pneumonia or hydrothorax; so the water seal was removed after the instillation of 200,000 units of penicillin into the thoracic cavity. The administration of oxygen was intermittently stopped to test the patient's tolerance. It was discontinued completely on the fifth postoperative day. On the eighth day it was noted that the medial aspect of the wound was slightly erythematous and extruded a small amount of purulent drainage. This subsided completely in a few days with application of hot wet dressings. On the sixteenth postoperative day the patient contracted chickenpox and was transferred to the Cook County Contagious Hospital. His stay there was uneventful, and he was returned to the pediatric medical ward on August 1 and was discharged from the hospital on August 3 in good condition, eating quite well and weighing 9 pounds 15 ounces

TABLE 1.—*Record of Examination of the Blood in Case 1*

Date	Hemoglobin Concentration, Gm.	Red Blood Cells, Millions	White Blood Cells	Color Index	Neutrophils	Eosinophils	Lymphocytes	Monocytes
4/24/48	15	7.97	10,650	0.60	43	1	55	1
5/14	15	7.33	11,000	0.68	56	..	40	4
5/15	15	7.13	.....	....	..	..	..	..
7/3 *	13	5.30	.....	....	..	..	..	..
7/5	2	5.47	.....	....	63	1	33	3
7/6	12	....	.....	....	..	..	..	..
7/10	9	5.41	13,500	1.0	..	..	..	..
7/13	9	4.82	13,500	0.56	52	6	42	..
8/3	10	5.80	12,850	0.57	40	2	51	7

* Day of operation.

(4,548 Gm.). The stethogram and electrocardiogram taken on August 2 showed the presence of a continuous murmur. There was no longer any visible cyanosis, and the blood count was within normal limits.

CASE 2.—E. R., a 5½ week old white male infant, was admitted to the cardiac service of the Cook County Children's Hospital on July 21, 1948, with the presenting complaints of dyspnea, rapid respirations of five weeks' duration and attacks of intermittent cyanosis of three weeks' duration.

He was born on June 10 by spontaneous, normal delivery, weighing 6 pounds 7½ ounces (2,934 Gm.). He manifested labored, rapid respirations from birth. Dr. Herman B. Lander studied this infant, made a provisional diagnosis of tricuspid atresia and transferred the baby to the Cook County Hospital for further examination.

The physical examination revealed a 5 week old cyanotic infant, weighing 6 pounds 11 ounces (3,033 Gm.), with severe dyspnea. Respirations were 70 per minute, pulse rate 160 and blood pressure 65 systolic and 35 diastolic. There was a prominent blueness of all mucous membranes, fingers, toes and the rest of the body. The femoral pulse was palpable.

The apex of the heart was in the fourth left interspace, just outside the midclavicular line. There was a harsh systolic murmur heard posteriorly all

over the precordium. The liver was palpable 2 fingerbreadths below the costal arch. At times, there seemed to be a slight pulsation of the edge of the liver.

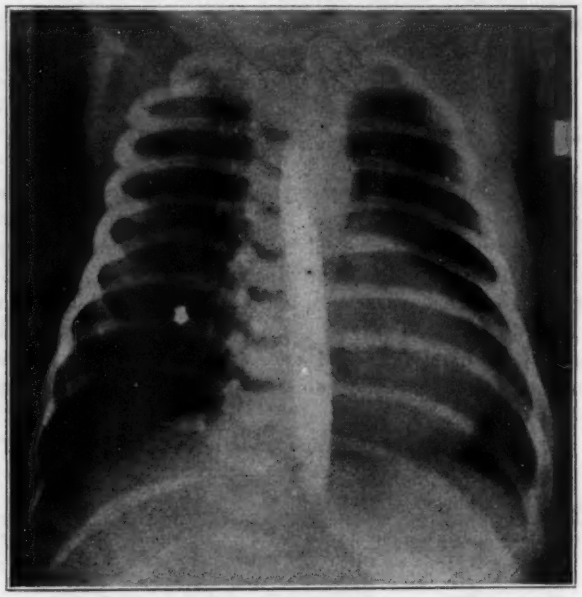

Fig. 6 (case 2).—Roentgenogram showing abnormal contour of right ventricle, clear pulmonary fields, narrow cardiac base and a left aortic arch.

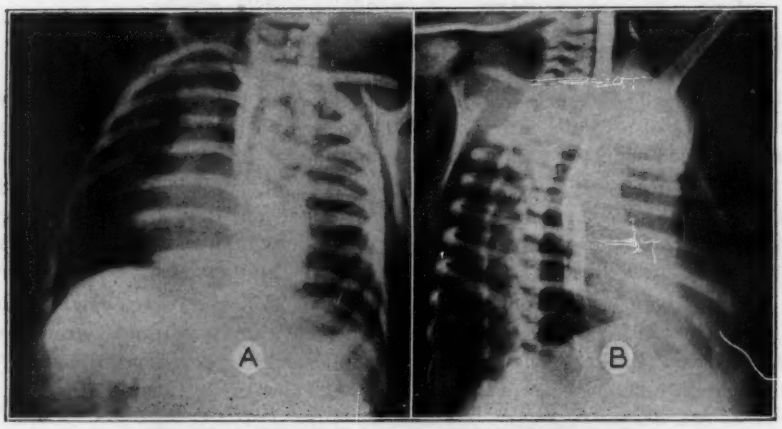

Fig. 7 (case 2).—Roentgenograms showing enlarged inflow tract of left ventricle, hypoplastic right ventricle and no deviation of the esophagus in (*A*) left oblique view, and posterior deviation of the esophagus in the region of the aorta and small right ventricle in (*B*) right oblique view.

The fluoroscopic examination revealed in the posteroanterior view a narrowing of the base of the heart and a cardiothoracic ratio of 50 per cent. The right border of the heart appeared unusually straight, with absence of the normal

contour of the right ventricle. The pulmonary conus showed a straight, flat line. The pulmonary fields were unusually clear, with no pulsations of pulmonary vessels. The left oblique view showed an enlargement of the inflow tract of the left ventricle and an absence or hypoplasia of the normal right ventricular contour. The pulmonary window was clear, and the right oblique view showed a straight pulmonary conus. The roentgenograms confirmed these findings, and the esophagram showed a normal deviation to the right, a posterior displacement in the right oblique view and no displacement in the left oblique view, i e., a normal left aortic arch.

The electrocardiogram showed a sinus tachycardia of 160, a left axis deviation with QRS complexes upright in lead I, small and diphasic in lead II and inverted

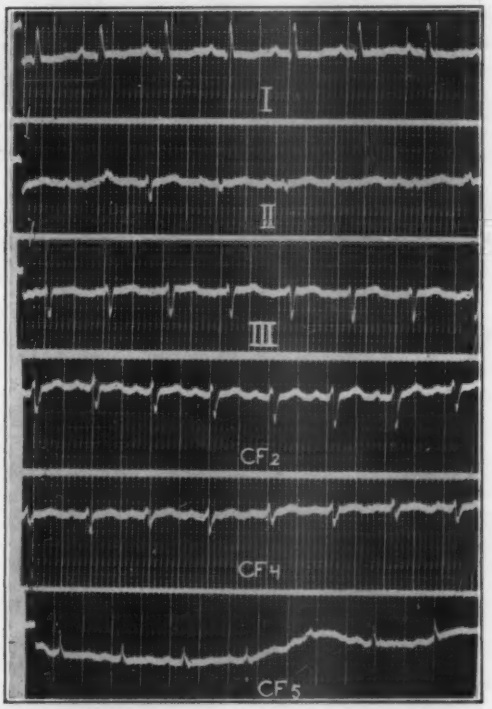

Fig. 8 (case 2).—Electrocardiogram showing a sinus tachycardia, QRS complex upright in lead I, small and diphasic in lead II and inverted in lead III. Chest leads show inversion in CF_2 and upright waves in CF_5.

in lead III. (The electrocardiographic findings were checked by Dr. A. L. Bohning.)

All these observations pointed to a diagnosis of tricuspid atresia, interauricular septal defect, hypoplastic right ventricle, pulmonary stenosis and either a patent ductus or an interventricular septal defect.

The infant was placed in an oxygen hood on July 21 and remained there until the operation was performed on August 6. In spite of the continuous administration of oxygen he continued to have many severe attacks of cyanosis. It was noted that as the infant became older he was more severely cyanotic and

seemed to have attacks which increased in intensity and frequency. He ate poorly and refused most feedings. It was, therefore, necessary to maintain his nutrition and hydration by parenteral administration of fluid.

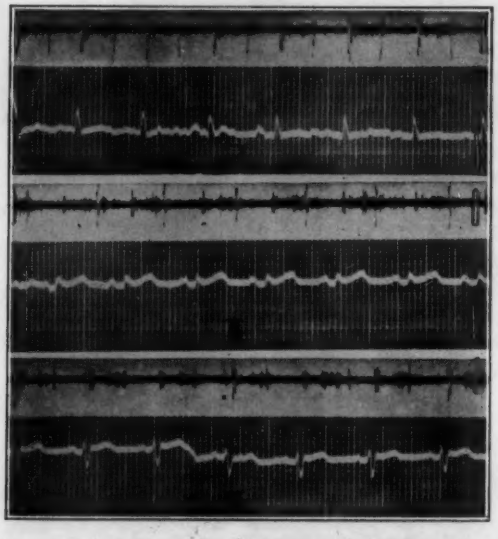

Fig. 9 (case 2).—Stethogram taken before operation showing systolic murmur over precordium.

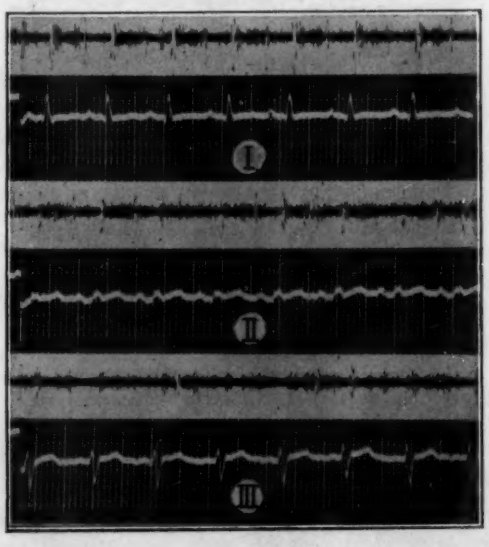

Fig. 10 (case 2).—Stethogram taken after operation showing systolic and diastolic murmur.

Operation was performed on August 6. The infant weighed 7 pounds 1 ounce. The night before surgical treatment he was given fluids orally until 2 a. m. Use of penicillin 20,000 units, was also started and given every three hours.

Atropine, 1/480 grain (0.18 mg.), was given before the operation. Anesthetization, with cyclopropane and oxygen, was started at 8:12 a. m. and stopped at 11:10 a. m.; the operation started at 8:50 a. m. and stopped at 11:10 a. m. The chest was opened through the fourth interspace, and it was necessary to resect a small portion of the fourth rib posteriorly in order to get an adequate approach. There were observed a small right ventricle and a pencil-sized aorta with a small pulmonary artery. A Potts-Smith-Gibson operation was performed, the anastomosis being 3 to 4 mm. in length. Closure was made with surgical gut for the subcutaneous tissues and silk for the skin. A water seal system was connected to a catheter in the thorax.

The patient's condition on returning to the ward was good. He was returned from the operating room with a portable oxgen hood and was immediately put into an oxygen tent with oxygen running at 10 liters per minute. The water seal system was connected and functioned quite well with a good initial negative pressure. The pulse rate was 150, respirations 35 and blood pressure 48 systolic and

TABLE 2.—*Record of Examination of the Blood in Case 2*

Date	Hemoglobin Concentration, Gm.	Red Blood Cells, Millions	White Blood Cells	Color Index	Polymorphonuclear Leukocytes	Eosinophils	Basophils	Lymphocytes	Monocytes
7/22/48	18.5	6.50	12,500	0.90	41	1	..	50	8
7/28	18	6.85	.....	....	..	..	..	..	..
8/2	17	6.90	7,850	0.88	74	..	..	28	1
8/6 *	..	....	.....	....	..	..	..	..	..
8/9	14.5	5.35	7,750	....	..	..	..	..	..
8/10	15	5.49	7,400	....	..	..	..	..	..
8/11	15	5.10	15,000	....	..	..	..	..	..
8/12	15	5.25	9,800	....	..	..	..	..	..
8/13	14.5	4.80	9,000	....	..	..	..	..	..
8/14	14	5.15	9,500	....	..	..	..	..	..
8/16	15	5.26	11,700	0.86	..	..	..	..	..
8/17	15	5.40	14,000	0.83	..	..	..	..	..

* Day of operation.

0 diastolic. He received 125 cc. of 5 per cent dextrose solution during the operation, and he was given 500 cc. of isotonic sodium chloride solution for the next twenty-four hours, running at fifteen drops per minute. Seconal sodium,* ½ grain (30 mg.) rectally, was given for restlessness. Examination with a portable x-ray machine made later in the day showed good expansion of both lungs. A good machinery murmur was audible in the left infraclavicular region immediately after surgical treatment. The patient started taking some fluids orally the first postoperative day. and thirty-six hours after the operation was given a dilute formula. He was taken out of the oxygen tent on the fourth postoperative day. The sutures were removed on the eighth postoperative day, and the postoperative course was uneventful. He was discharged from the hospital on August 29. There was no visible cyanosis or dyspnea. A continuous murmur was heard over the precordium, and the blood count was within normal limits.

COMMENT

Two infants, one 7 weeks old, weighing only 7 pounds 1 ounce, and the other 6 months of age, weighing 8 pounds 11 ounces on the

day of the operation, were carefully studied, and the diagnosis of tricuspid atresia with a pulmonary stenosis appeared certain. Both were desperately ill patients, extremely cyanotic and dyspneic even while in an oxygen tent. The enlargement of the left ventricle, shown by fluoroscopy and roentgenograms, and confirmed by the electrocardiogram, and the presence of a small right ventricle meant that pulmonary stenosis must also be present, because there cannot be a good normal pulmonary artery coming off a nonfunctioning or hypoplastic right ventricle. The pronounced concavity of the pulmonary conus in the anteroposterior and the right oblique views, and the unusually clear pulmonary fields without visible pulsations of the pulmonary vessels, as well as the wide and clear pulmonary window, pointed to this diagnosis.[4]

In the presence of tricuspid atresia, blood entering the right auricle must flow into the left auricle, through either a patent foramen ovale or an interauricular septal defect. From the left auricle blood enters the left ventricle and the aorta. The only way blood can enter the lungs is through either a patent ductus arteriosus or an interventricular septal defect. In one of our unpublished cases of tricuspid atresia, definite pulmonary pulsations were noted in the hilus and pulmonary fields. This means a good or even excessive blood supply to the lungs, i.e., an additional malformation. The pulmonary artery was transposed and came off the left ventricle. We advised against an operation in this case, and the observations at autopsy confirmed our contention.

There was no question about the diagnosis for these 2 infants. Every one concerned with the infants knew that they would die if treated only medically. We decided to give the infants the only chance they had.

Their response following the anastomosis of the aorta to the pulmonary artery, as shown by the disappearance of the visible cyanosis, dyspnea and polycythemia and by their increased vigor in feeding and gain in weight, was striking. The clinical results achieved in these patients suggest that any cyanotic infant whose congenital malformation is amenable to surgical treatment, no matter how young and debilitated he may be, should not be allowed to die of anoxemia, but should be given the benefit of a Potts-Smith-Gibson operation.

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4. The generally accepted statement that a patient with definite cyanosis and left axis deviation must have tricuspid atresia and hypoplastic right ventricle is not entirely true. Gasul, Richmond and Krakauer will report a case of an extremely cyanotic child with a definite left axis strain, as shown by roentgenograms and an electrocardiogram, whose autopsy revealed tetralogy of Fallot with patent foramen ovale.

CONCLUSIONS

1. Two extremely cyanotic, dyspneic infants, one only 7 weeks old, weighing 7 pounds 1 ounce, the youngest on record, and the other 6 months of age, weighing 8 pounds 11 ounces, were successfully operated on for tricuspid atresia and pulmonary stenosis.

2. Surgical intervention may be indicated even in very young infants, so long as the diagnosis reveals a congenital malformation amenable to surgical treatment and the clinical course indicates that early intervention is desirable.

NOTE.—A third, desperately ill infant 3 months of age with tricuspid atresia has recently been successfully operated on at the Cook County Children's Hospital.

4753 Broadway (Dr. Gasul).

5 S. Wabash Avenue (Dr. Fell).

ANOXIA OF THE CENTRAL NERVOUS SYSTEM AND CONGENITAL HEART DISEASE

Report of Three Cases with a Note on the History of Asphyxia

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ALLUSION to asphyxia weaves through the history of medicine. Yesterday's percepts have converged and cumulated in today's concept of anoxemia with its ultimate cerebral lesion.

Antiquities.—The Edwin Smith papyrus—the oldest known medical treatise, which was written possibly around 3000 B. C. by the Egyptian physician, Imhotep—mentions the brain for the first time on record and declares it to be the seat of nervous and mental functions under the control of respiration.[1] This pneumatic notion undoubtedly influenced the Hebrews during their captivity in Egypt. The first book of the Bible, "Genesis," refers to the breath of life.[2] Ezekiel, while viewing the carnage of battle, was constrained to cry, "Come from the four winds, O breath, and breathe upon these slain that they may live."[3] The composer of the Psalms deflated man in the verse, "His breath goeth forth, he returneth to his earth; in that very day his thoughts perish."[4]

One of the first oriental classics—"Huangti," Neiching (2697 B. C.?), the basis of Chinese medicine—proclaimed the lungs as executors of the heart and the storehouse of energy-giving breath.[5] Early Sanskrit documents of the Hindus, the "Rig Veda" (1500 B. C.) and the "Atharva Veda," suggested theses for later Brahmin priests and scholars. Of these, Susruta (fifth century A. D.) compiled a monumental work on Aryan surgery in which, among other ideas in physi-

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1. (*a*) Breasted, J. H.: The Edwin Smith Surgical Papyrus, Chicago, University of Chicago Press, 1930, vol. 1, pp. 12, 37, 45, 50, 125, 164-174 [case 6], 202. (*b*) Castiglioni, A.: A History of Medicine, translated from the Italian and edited by E. B. Krumbhaar, New York, Alfred A. Knopf, Inc., 1941, pp. 55-57.

2. Genesis 2:7; 6:17; 7:22.

3. Ezekiel 37:5, 9.

4. Psalms 146:4.

5. Hsieh, E. T.: A Review of Ancient Chinese Anatomy, Anat. Rec. **20**:97, 1921.

ology, he presupposed that all vital phenomena below the navel are activated by means of air.[6]

Breath, life and the cranial contents are correlated in the Babylonian epic, "Enûma elisk," which gives a graphic account of the disease-overcoming god, Marduk, and his skull-splitting club.[7] Mesopotamian priests, who thought that the liver was the center of blood supply and of life,[8] collected clinical data which they could use as omens or tokens of recovery or death.[9] Their classified symptomatology included breathing that "gives sound like a flute."[10] Ancient Assyrians prevented the pain of circumcision by compressing the carotid arteries long enough to produce temporary cerebral hypoxia and stupor.[11]

Assuming that life resided in the breath, the Homeric writer (dating back to 1000 B. C.) referred tacitly to brain injuries with their attendant neurologic symptoms, alterations in respiration and fluctuations of consciousness. Antilochos drove his spear into the brow of a Trojan warrior: ". . . the point of bronze passed within the bone; darkness clouded his eyes . . . so his life departed from him." Sarpedon, son of Zeus, severely wounded in the thigh, sat beneath an oak:

> . . . his spirit failed and mist overspread his eyes. Then breathed he again, and the breath of the north wind blew round about him and brought him to life from the grievous swoon of his soul.

On several occasions the wounded and gasping Hector "gat back his breath" before "black night covered his eyes."[12]

Greco-Roman Era.—Pythagoras (580-489 B. C.), founder of the Italian school of philosophers, is credited with being the first to locate the center of higher activities in the brain, and his Greek pupil Alcmaeon

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6. Hoernie, A. F. R.: Studies in the Medicine of Ancient India, Oxford, Clarendon Press, 1907, sect. 5b, pp. 63-65.

7. Heidel, A.: The Babylonian Genesis: The Story of Creation, Chicago, University of Chicago Press, 1942, pp. 29, 32, 89, 93 and 125.

8. Jastrow, M.: The Medicine of the Babylonians and Assyrians, Proc. Roy. Soc. Med. (Sect. Hist. Med.) **7**:109, 1914; The Signs and Names for the Liver in Babylonian, Ztschr. f. Assyriol. **20**:105, 1907. Ezekial 21:21.

9. Neuburger, M.: Geschichte der Medizin, Stuttgart, F. Enke, 1906, vol. 1, p. 31.

10. Castiglioni,[1b] pp. 37-44.

11. Hoffmann, C.: De thorace, ejusque partibus commentarius tripartitus, Frankfurt, apud D. Aubrios et c. Schleichium, 1627, book 2, chap. 29, p. 77.

12. Homer: The Complete Works of Homer: The Iliad, translated by A. Lang, W. Leaf and E. Meyers, New York, Modern Library, Inc., 1935, book 4, pp. 72 and 132; book 5, p. 94; book 11, p. 195; book 14, p. 262; book 15, p. 266; book 16, p. 302; book 22, p. 410; The Odyssey, translated by S. H. Butcher and A. Lang, ibid., book 9, p. 134; book 11, p. 168.

stated that nerves are derived therefrom.[13] By dissociating medicine from theurgy, human fantasy and the whim of gods, Hippocrates (460-370 B. C.) opened the way for scientific investigation of respiration. Aristotle (384-322 B. C.), apparently the first to write about breathing difficulties at high altitudes, stated that man could not live on Mount Olympus due to thinness of the air.[14] Erasistratus (310-250 B. C.) believed that air from the lungs diffused into the heart and was carried to the cerebral ventricles where the vital spirit was transformed into the animal spirit which was then transmitted by the nerves to the various parts of the body.[15] Asclepiades (124 B. C.) taught that continuously moving atoms of the atmosphere penetrated the organism through the lungs and were driven with the blood to all anatomic structures, and that any disturbance in their regular flux caused disease.[16] Celsus (25 A. D.) recommended a frequent change of air in the rooms of patients with pneumonia.[17] Galen (131-201 A. D.), who believed that the object of breathing was to cool the fiery heart, called attention to the noxious fumes in the copper sulfate mines of Cyprus and explained the "ebb and flow" dynamics of respiration and circulation by teaching that blood passed from the right ventricle of the heart to the left through invisible passages in the ventricular septum.[18]

Medieval Ebb.—Although faulty and inaccurate, Galen's work was so tremendous that the weight of his authority halted progress in medical discipline, and nothing was learned about asphyxia or respiratory physiology for the next one and a half millenniums. During this interval the tender science was inefficiently refrigerated in the Byzantine Empire, in the Islamic caliphates of Baghdad and Córdova, in the monasteries of Benedictine monks, in the school of Salernitan physicians and in the cloisters of copyists and translators of Jewish and Arab manuscripts. Medicine was thus duly contaminated with the effemination of Eastern Romans, the theomagy of Arabs and Jews and the garblings of literary hacks. Throughout these centuries the hippocratic art was in the hands of hierophants: druids of England, priests of Europe, wolfmen of Russia. By the sixteenth century the medical pro-

13. Mieli, A.: Le Scuole Ionica, Pythagorica ed Eleata (I Prearistotelici, I), Firenze, Libreria della Voce, 1916, chap. 2, pp. 331, 332 and 340.

14. Thompson, D. W.: On Aristotle as a Biologist, Oxford, Clarendon Press, 1913, p. 23.

15. Fuchs, R.: Erasistratea, quae in librorum memoria latent, congesta enarrantur, Inaug. Dissert., Berlin, Fock, 1892.

16. Choulant, L.: Der Rath des Asclepiades, Allg. med. Ann., 1824, pp. 577-584. Castiglioni,[1b] pp. 196-201.

17. Celsus, A. C.: De Medicina libri octo, translated by J. Greive, London, D. Wilson & T. Durham, 1756, book 4, chap. 7, pp. 204-205.

18. Foster, M.: Lectures on the History of Physiology During the Sixteenth, Seventeeth and Eighteenth Centuries, Cambridge, 1901, pp. 12 and 13.

fession had sunk to an all-time low. The unclassed hordes of "wandering cataract couchers, lithotomists, herniotomists, and booth-surgeons" were, in the words of William Clowes, a contemporary English surgeon, no better than "vagabonds . . . shameless in countenance, lewd in disposition, brutish in judgment and understanding." Quackery, rampant everywhere, was practiced by

> . . . tinkers, tooth-drawers, peddlers, ostlers, carters, porters, horse-gelders and horse-leeches, idiots, apple-squires, broom-men, bawds, witches, conjurers, sooth-sayers and sow-gelders, rogues, rat-catchers, runagates, and proctors of spittle-houses. . . .[19]
>
> Sober quacks of ponderous mien solemnly diagnosed everything from disappointed love to measles by naked eye examination of a flask of the sufferer's urine.[20]

Renaissance.—While riding the crest of this wave of intellectual deterioration, Galen's pronouncements, regarded by the entire world as indisputable canon and aureoled by the church as true dogma, collided with terrific impact against the swarthy and doughty figures of Jean Fernel (1497) and Andreas Vesalius (1514). These impetuous physicians braced off against accepted teachings, tossed tradition to the winds, dragged the Galen-idol down and, with sweeping violence, scorn and heresy, turned their backs to the dust dunes of the ages. Their gigantic fortitude enabled humanity to lift its hands to the green horizon of an epoch in medicine. For example, Vesalius, in direct refutation of Galen, showed that artificial respiration could maintain the life of an animal after its thorax had been opened and its lungs collapsed. In a fit of iconoclasm he wrote about the hypothetic pores in the ventricular septum, "We are driven to wonder at the handiwork of the Almighty by means of which the blood sweats from the right into the left ventricle . . ."[21] Reverence, nevertheless, tempered the élan of the young anatomist. He said, "I am almost as afraid to argue about Galen's authority as I would be to doubt the immortality of the soul in our holy religion."[22] Although incriminated for their honest thought, this audacious scientist and his confrères hurled down many barriers against progress in medicine. And once again, respiratory physiology and asphyxia legitimately claimed the attention of investigators.

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19. Garrison, F. H.: History of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1921, pp. 231 and 233.

20. Long, E. R.: A History of Pathology, Baltimore, Williams & Wilkins Company, 1928, p. 64.

21. Vesalius, A.: Suorum de humani corporis fabrica librorum epitome, Basel, J. Oporini, 1543, book 6. Garrison,[19] pp. 213 and 214.

22. Cushing, H.: A Bio-Bibliography of Andreas Vesalius, New York, Schuman's, 1943, p. 57.

Observations on Breathing.—Passages from Agricola's "De re metallica" described in striking clinical terms the effects of inhaling pernicious gases in the mine pits.[23] While in the high Andes "where the aire and the wind make men dazie," a Jesuit priest, Joseph deAcosta (1588), ascribed the acutely distressing symptoms of himself and fellow travelers to a "subtile and delicate element of the aire . . . The griefs wee feele comes from the quality of the aire wee breathe."[24] After nearly four centuries, Monge (1943), while working in the same locale, recognized not only the acute phase but also the subacute and chronic forms of mountain sickness.[25] By using the newly invented decompression chamber, Robert Boyle (1660) proved that air was necessary for the life of animals and also for combustion.[26] Robert Hooke (1665, 1667) gave the first description of the cellular nature of plant tissue[27] and repeated Vesalius' experiment in order to convince himself that a dog really could be kept alive by "Reciprocal blowing up of his Lungs with Bellowes" after the thorax had been opened and immobilized.[28] Descartes (1662), harking back to Erasistratus, thought that animal spirits from the air were carried, by way of the ventricles of the brain and nerve tubules, to the muscles which relaxed or contracted according to the quantity of these spirits.[29] Believing that "igneo-aerial" particles were absorbed into the blood from the lungs, Lower (1669) and Mayow (1674) argued that maternal blood must supply the fetus with these color-giving particles, as well as with food.[30]

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23. Agricola, G.: De re metallica: De natura eorum quae effluent ex terra, in Balneis (de) omnia quæ extant apud Græcos, Latinos et Arabas, tam medicos quam quoscunque ceterarum artium probatos scriptores, fol. Venetiis, Juntas, book 4, 1553, pp. 273-278.

24. deAcosta, J.: The Naturall and Morall Historie of the East and West Indies, London, V. Sims for E. Blount and W. Asplay, 1604, book 3, chap. 9, in Major, R. H.: Classic Descriptions of Disease, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1945, pp. 553-555.

25. Monge, C.: L'erythrémie des altitudes, Bull. Acad. de. med. **101**:562 (April 30) 1929; Chronic Mountain Sickness, Physiol. Rev. **23**:166 (April) 1943.

26. Boyle, R.: New Experiments Physico-Mechanicall Touching the Spring of the Air, and Its Effects, Oxford, H. Hall, 1660, pp. 350-352.

27. Hooke, R.: Micrographia, London, J. Martyn & J. Allestry, 1665.

28. Hooke, R.: An Account of an Experiment of Preserving Animals Alive by Blowing Through Their Lungs with Bellows, Phil. Tr. Roy. Soc. **2**:539, 1667.

29. Descartes, R.: De homine figuris et latinate donatus a Florentio Schuyl, Lugd. Bat., apud F. Moyardum & P. Leffen, 1662, in Fulton, J. F.: Selected Readings on the History of Physiology, Springfield, Ill., Charles C Thomas, Publisher, 1930, pp. 236-240.

30. Lower, R.: Tractatus de corde, item de motu et colore sanguinis et chyli in eum transitu, London, J. Allestry, 1669, p. 86. Mayow, J.: De Respiratione, in Tractatus quinque medico-physici: Tertius de respiratione fœtus in utero, et ovo, ed. 2, Oxonii, e theatro Sheldiano, 1674, Tractatus II.

Respiratory Gases.—Although the Jewish "Talmud" of the Babylonian era had likened respiration to burning,[31] it was not until 1754 that Joseph Black discovered the "fixed air" (carbon dioxide) given off by the lungs.[32] Twenty years later, Joseph Priestly (1774) noted that the "dephlogisticated air" (oxygen) which he had isolated disappeared both in combustion and in animal respiration and was produced by green plants.[33] He also prepared nitrous oxide, which Sir Humphry Davy (1800) found helpful, when inhaled, in relieving pain caused by an erupting wisdom tooth.[34] Davy suggested that the gas "may probably be used with advantage during surgical operations."[35] Laurent Lavoisier (1775), with the astronomer La Place (1780, 1785), demonstrated that carbon dioxide is formed in the burning process by the union of carbon with oxygen and is produced in respiration—analogue of combustion—in volumes approximately equal to the amount of oxygen consumed.[36]

THE MODERN ERA

The nineteenth century abounded in medical discoveries and adoptions into medicine of innovations in other branches of science. Botany donated the cellular hypothesis whereby the 25 year old Rudolf Virchow[37] disposed, with one vicious fell swoop, of von Rokitansky's system of humoral pathology with its "crases" and "dyscrases."[38]

31. Preuss, J.: Biblisch-talmudische Medizin: Beiträge zur Geschichte de Heilkunde und der Kultur überhaupt, Berlin, S. Karger, 1911. Garrison,[19] p. 61.

32. Black, J.: De humore acido a cibis orto, et magnesia alba, Edinburgh, G. Hamilton et J. Balfour, 1754.

33. Priestly, J.: Experiments and Observations on Different Kinds of Air, London, J. Johnson, 1774, pp. 43-54.

34. Davy, H.: Researches, Chemical and Philosophical, Chiefly Concerning Nitrous Oxide, or Dephlogisticated Air, and Its Respiration, London, Smith, Elder & Co., 1839, p. 276.

35. Garrison,[19] p. 540. Davy,[34] p. 329.

36. Lavoisier, A. L.: Memoire sur la nature du principe qui se combine avec les métaux pendant leur calcination et qui en augmente le poids, Hist. Acad. roy. d. Sc. (1775), 1778, p. 520-526; Expériences sur la respiration des animaux et sur les changemens qui arrivent à l' air en passant par leur pouman, ibid. (1777) 1780, p. 185. Lavoisier, A. L., and La Place, P. S.: Mémoire sur la chaleur, ibid. (1780) 1784, p. 355; Mémoire sur quelques fluides qu'on peut obtenir dans l'état aériforme, Mém. Acad. roy. d. Sc., 1780, pp. 337 and 355.

37. Virchow, R.: Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre, Berlin, A. Hirschwald, 1858; translated by F. Chance, New York, R. M. DeWitt, 1860, pp. 27-50.

38. von Rokitansky, C.: Lehrbuch der pathologischen Anatomie, Vienna, W. Braumüller u. Seidel, 1842-1846; translated by W. E. Swaine, London, J. F. Adlard, 1854, vol. 1, pp. 362-410.

Neurohistology, thus, became free to clarify neurologic and mental phenomena.

Respiratory Physiology.—Scattered observations now began to elucidate a few of the mysteries of respiration. In 1791, Hassenfratz detected carbon dioxide in blood returning from the tissues.[39] Legalloise (1811) observed that respiratory failure and death followed destruction of a small portion of the medulla oblongata in the floor of the fourth ventricle.[40] Clissold (1823) concluded that debility in mountain climbers was due to oxygen reduction in the atmosphere at high altitudes.[41] Flourens (1837) located the "vital node," the bilateral center of respiration in the medulla, and showed that lesions thereof cause asphyxia.[42] In 1842, Stanley inaugurated the study of deleterious effects of nitrous oxide anesthesia.[43] Gustav Magnus (1837, 1845), having found a way to liberate gases from blood by exposing it to a vacuum (suggested by Boyle), gathered less oxygen and more carbon dioxide from venous blood than from arterial blood and deduced from his experiments that the oxygen–carbon dioxide exchange occurs in the tissues.[44] In 1856, Matteucci noticed not only that muscles respire and generate heat but that their activity is accompanied with electrical changes.[45] Meyer (1857) recognized that oxygen must be held in the blood by some kind of chemical affinity,[46] a point postulated by

39. Hassenfratz, J. H.: Mémoire sur la combinasion de l'oxigène avec le carbone et l'hydrogène du sang, sur la dissolution de l'oxigène dans le sang, et sur la manière dont le calorique se dégage, Ann. d. Chim. **9**:261, 1791.

40. Legalloise, C. J. J.: Expériences sur le principe de la vie, notamment sur celui des mouvemens du cœur, et sur le siége de ce principe, Paris, D'Hautel, 1812, p. 37.

41. (*a*) Clissold, F.: Notice sur une nouvelle ascension au mont Blanc, Biblioth. Univ. de Geneve **21**:68, 1822-1823. (*b*) Bert, P.: La pression barométrique: Recherches de physiologie experimentale, Paris, G. Masson, 1878, translated by M. A. Hitchcock and F. A. Hitchcock, Columbus, Ohio, College Book Company, 1943, pp. 223-224.

42. Flourens, M. J. P.: Recherches expérimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébrés, ed. 2, Paris, J. B. Baillière, 1842, p. 204; Détermination du noeud rital ou point premier moteur du mécanisme respirtoire dans les vertébrés à sangfroid, Comp. rend. Acad. d. sc. **51**:314-317, 1862.

43. Stanley, F.: Poisoning by the Inhalation of Impure Nitrous Oxide Gas, Lancet **1**:395, 1842-1843.

44. Magnus, H. G.: Ueber die im Blute enthaltenen Gase, Sauerstoffe, Stickstoff und Kohlensäure, Ann. d. Phys. u. Chem. **12**:583, 1837.

45. Matteucci, C.: Cours d'électrophysiologie, professé à l'Université de Pise en 1856, Paris, Mallet-Bachelier, 1858, vol. 11, chap. 12.

46. Meyer, L.: Die Gase des Blutes, Inaug. Dissert., Göttingen, Dieterich, 1857, pp. 54 and 56.

von Liebig in 1851,[47] and Hoppe-Seyler (1862) attributed this union to the hemoglobin of red corpuscles.[48]

Discoveries in the physiology of respiration and asphyxia followed in rapid succession. In 1868, Hering and Breuer noticed that inflation of the lungs inhibited inspiration, whereas deflation inhibited expiration.[49] Henry Head (1869) observed similarities in function between a steam engine governor, which regulates the expenditure of power, and the vagus nerves, which economize the energies of respiration.[50] From 1869 to 1872, Goltz put the theory of Pythagoras to experimental proof and demonstrated clearly not only that the brain is the center of higher activities but that decerebration becomes more profound in its effects the higher the animal, resulting in amentia in man.[51] From 1866 to 1878, Pflüger, with Ludwig and Meyer,[52] established the basic mechanism of respiration: oxygen diffuses into venous blood of the lungs, forms an easily dissociable compound with hemoglobin and is carried in arterial blood to the tissues, where it is partially absorbed; carbon dioxide, entering the venous blood of tissue capillaries, is transported to the lungs, where it is expired.[53]

Asphyxia Due to High Altitude.—Man's interest in exploring the upper regions of the atmosphere led some workers at this time to study the effects of high altitudes on physiologic processes. During the latter part of a balloon ascent with Sivel and Crocè-Spinelli, Tissandier (1875) at 24,600 feet recorded his feelings of inward joy, no thought of danger and gladness to be rising. He stated, "At 26,000 feet my tongue was paralyzed. All at once I shut my eyes and fell powerless and lost all further memory." The writer of those words survived an

47. von Liebig, J.: Familiar Letters on Chemistry, in Its Relation to Physiology, Dietetics, Agriculture, Commerce, and Political Economy, ed. 3, London, Taylor, Walton & Maberly, 1851, vol. 20, p. 536.

48. Hoppe-Seyler, E. F.: Einwirkung des Schwefelwasserstoffgases auf das Blut, Centralbl. f. d. med. Wissensch. **1**:433, 1863. Castiglioni,[1b] p. 780.

49. Hering, E., and Breuer, G.: Die Selbststeuerung der Athmung durch den Nervus Vagus, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **57**:672, 1868.

50. Head, H.: On the Regulation of Respiration, J. Physiol. **10**:1 and 279, 1889.

51. Goltz, F. L.: Beiträge zur Lehre von den Functionen der Nervencentren des Frosches, Berlin, A. Hirschwald, 1869; Ueber den Einfluss der Nervencentren auf die Aufsaugung, Arch. f. d. ges. Physiol. **5**:53, 1872; Ueber die Functionen des Lendenmarks des Hundes, ibid. **8**:460, 1874.

52. Garrison,[19] p. 608.

53. Pflüger, E. F. W.: Zur Gasometrie des Blutes, Centralbl. f. d. med. Wissensch. **4**:305, 1866; Ueber die Ursache der Athembewegungen, sowie der Dyspnoë und Apnoë, Arch. f. d. ges. Physiol. **1**:61, 1868; Ueber die Diffusion des Sauerstoffs, den Ort und die Gesetze der Oxydationsprocesse im thierischen Organismus, ibid. **6**:43 and 190, 1872. Pflüger, E. F. W. and Finkler, D.: Beiträge zur Lehre von der Respiration, ibid. **10**:251, 1875. Pflüger, E. F. W.: Ueber Wärme und Oxydation der lebendigen Materie, ibid. **18**:247, 1878.

elevation of over 28,000 feet, but his companions in the gondola were dead when the balloon descended.[54] Paul Bert (1878) published the results of his experiments with a balloon and decompression chamber and portrayed clinical effects due to inhalation of rarefied air. He procured evidence to prove that symptoms—impairment of emotional control, reason, judgment, memory and the performance of special senses, along with exaggerated self esteem and boisterousness—are due to decreased oxygen.[55] Mosso and Marro (1903), while studying the relation of barometric pressure to respiration, became persuaded that symptoms at high altitudes result from nearly complete absence of carbon dioxide (acapnia).[56] However, Haldane and his associates (1919) affirmed the contention of Clissold that aerial sickness is due to diminished partial pressure of oxygen and that "anoxemia not only stops the machine but wrecks the machinery."[57] In describing the intoxicating effects of high altitudes, Barcroft (1920, 1923) stated that some of his well disciplined men quarreled, became restless, garrulous and morose, vomited and flung their arms about on the ledge of a crevasse, much to the embarrassment of his guide. He described three types of anoxia, based on functional disturbances in the physiology of respiration, and classified them as anoxic (diminished oxygen intake), anemic (diminished oxygen-carrying capacity of the blood) and stagnant (diminished rate of blood circulation).[58] Later (1931), Peters and Van Slyke added a fourth type, histiotoxic anoxia as in cyanide poisoning, in which the respiratory mechanism of the cells themselves is impaired.[59]

Control of Respiration.—The classic experiments of Marckwald (1887) laid the foundation of knowledge concerning the exact location of nervous structures controlling respiration. This worker concluded that a center, inhibitory to respiration and augmented by vagal influence, existed somewhere in the brain stem behind the inferior colliculi.[60]

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54. Tissandier, G.: La Nature, Paris, 1875, pp. 337-344. Bert, [41b] pp. 961-1007.

55. Bert,[41b] pp. 241-242, 363-366, 372-373, 377-381, 666-669 and 673-675.

56. Mosso, A., and Marro, G.: L'acapnie produite chez l'homme par la diminution de la pression barométrique, Arch. ital. de biol. **39**:387, 1903.

57. Haldane, J. S.: Anoxæmia, Brit. M. J. **2**:65 (July 19) 1919.

58. Barcroft, J.: Anoxæmia, Lancet **2**:485 (Sept. 4) 1920. Barcroft, J., and others: Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body Carried Out in the Peruvian Andes, Chiefly at Cerro de Pasco, Tr. Roy. Soc. B **211**:351, 1922-1923.

59. (*a*) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 579. (*b*) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, p. 358.

60. Marckwald, M.: Die Athembewegungen und deren Innervation beim Kaninchen, Ztschr. f. Biol. **5**:149, 1887; Die Bedeutung des Mittelhirns für die Athmung, ibid. **8**:259, 1890.

This conclusion was confirmed in 1939 by Pitts, Magoun and Ranson who accurately located the inspiratory and expiratory centers in the reticular formation of the medulla oblongata of the cat.[61] Evidence for automaticity of the respiratory center in a cold-blooded species was obtained by Adrian and Buytendijk in 1931.[62]

In 1905, Haldane and Priestley observed that a rise of only 0.2 per cent in the carbon dioxide content of alveolar air was sufficient to double pulmonary ventilation in man.[63] Christiansen, Douglas and Haldane (1914) first suggested that carbon dioxide from tissues enters erythrocytes where, in a chemical reaction catalyzed by carbonic anhydrase, it combines with water to form carbonic acid, which in turn reacts with a base to form bicarbonate. This process is made possible, these workers stated, because hemoglobin—most important of the weak acids of the blood—becomes weaker in its acidity after it has lost some of its oxygen to the tissues and is thus forced to yield a portion of its base to carbonic acid. In the lungs, hemoglobin is reoxygenated, increases in acidity and again becomes quite able to displace carbonic acid which then decomposes to liberate carbon dioxide into alveoli.[64]

Dreyer (1919) and West (1920) showed that vital capacity, the total amount of air which can be exhaled after a maximum inhalation, has a consistent relationship to the surface area of the body.[65] In 1925, Warburg first recognized the importance of an iron-porphyrin substance in intracellular metabolism and gave it the name "oxygen-transferring enzyme."[66] In reviewing respiratory oxidations, Proger (1943) posed the complicated process that probably involves numerous enzymes, coenzymes and respiratory catalysts, among which may be

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61. Pitts, R. F.; Magoun, H. W., and Ranson, S. W.: Localization of the Medullary Respiratory Centers in the Cat, Am. J. Physiol. **126**:673 (July) 1939; Interrelations of the Respiratory Centers in the Cat, ibid. **126**:689 (July) 1939; The Origin of Respiratory Rhythmicity, ibid. **127**:654 (Nov.) 1939.

62. Adrian, E. D., and Buytendijk, F. J. J.: Potential Changes in the Isolated Brain Stem of the Goldfish, J. Physiol. **71**:121 (Feb.) 1931.

63. Haldane, J. S., and Priestley, J. G.: The Regulation of the Lung-Ventilation, J. Physiol. **32**:224 (May) 1905.

64. Christiansen, J.; Douglas, C. G., and Haldane, J. S.: The Absorption and Dissociation of Carbon Dioxide by Human Blood, J. Physiol. **48**:244 (July) 1914.

65. Dreyer, G.: The Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227 (Aug. 9) 1919. West, H. F.: Clinical Studies on Respiration: A Comparison of the Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

66. Warburg, O.: Iron, the Oxygen Carrier of Respiratory Ferment, Science **61**:575 (June) 1925; The Chemical Constitution of Respiratory Ferment, ibid. **68**:437 (Nov.) 1928.

mentioned the cytochromes, the C_4-dicarboxylic acids, flavoproteins and pyridine nucleotides.[67]

The carotid reflex was described in 1927 by Heymans and Heymans, who ascertained the existence of pressoreceptors among collagenous fibers of the wall of the carotid sinus which can be stimulated by mechanical means, such as stretching, to inhibit respiratory activity. Chemoreceptors, assumed to lie in the glandlike aortic and carotid bodies and possibly glomus jugularis, can be stimulated by chemical means, such as anoxemia, to increase the rate and depth of respiration.[68]

Van Allen, Lindskog and Richter (1930) produced considerable anatomic and physiologic evidence for a mechanism of intra-alveolar communication, either through the vents of Kohn or by rapid air diffusion, the object of which is the adequate and uniform distention of pulmonary alveoli—even in case of bronchial obstruction.[69] While investigating the anatomy of pulmonary alveoli, Josselyn (1935) and others suggested that alveolar membranes may be discontinuous, that in places blood may be separated from alveolar air only by capillary endothelium.[70]

In 1937, Snyder and Rosenfeld collected convincing data concerning fetal respiratory movements and their ready inhibition by anoxemia and drug narcosis.[71]

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67. Proger, S.: The Use of Respiratory Catalysts, Particularly Succinic Acid, in Tissue Anoxia, Bull. New England M. Center **5**:80 (April) 1943. A Symposium on the Respiratory Enzymes, Madison, Wis., University of Wisconsin Press, 1942.

68. Heymans, J. F., and Heymans, C.: Sur les modifications directes et sur la regulation reflexe de l'activite du centre respiratoire de la tête isolée du chien, Arch. internat. de pharmacodyn. et de thérap. **33**:273, 1927. Winship, T.; Klopp, C. T., and Jenkins, W. H.: Glomus Jugularis Tumors, Cancer **1**:441 (Sept.) 1948.

69. Van Allen, C. M.; Lindskog, G. E., and Richter, H. G.: Collateral Respiration: Transfer of Air Collaterally Between Pulmonary Lobules, J. Clin. Investigation **10**:559 (Aug.) 1931; Gaseous Interchange Between Adjacent Lung Lobules, Yale J. Biol. & Med. **2**:297 (March) 1930. Lindskog, G. E., and Van Allen, C. M.: Aerodynamics of Bronchial Obstruction, Arch. Surg. **24**: 204 (Feb.) 1932.

70. Josselyn, L. E.: The Nature of the Pulmonary Alveolar Lining, Anat. Rec. **62**:147 (May) 1935. Willson, H. G.: The Terminals of the Human Bronchiole, Am. J. Anat. **30**:267 (May) 1922. Macklin, C. C.: Functional Aspects of Bronchial Muscle and Elastic Tissue, Arch. Surg. **19**:362 (Dec.) 1929; The Dynamic Bronchial Tree, Am. Rev. Tuberc. **25**:393 (March) 1932; Pulmonic Alveolar Vents, J. Anat. **69**:188 (Jan.) 1935.

71. Snyder, F. F., and Rosenfeld, M.: Direct Observations of Intrauterine Respiratory Movements of the Fetus and Role of Carbon Dioxide and Oxygen in Their Regulation, Am. J. Physiol. **119**:153 (May) 1937; Breathing of Amniotic Fluid as Normal Function of Fetal Respiration, Proc. Soc. Exper. Biol & Med. **36**:45 (Feb.) 1937; Intrauterine Respiratory Movements of the Human Fetus, J. A. M. A. **108**:1946 (June 5) 1937. Dick, F., Jr., and Pund, E. R.: Asphyxia Neonatorum and the Vernix Membrane, Arch. Path. **47**:307 (April) 1949.

Dixon (1937), Burk (1939), Johnson (1941) and Lipmann (1941) discussed the anaerobic mechanism (Pasteur effect) which becomes operative in tissues under strain until the supply of oxygen has been adjusted to the increased demands for energy. When present in adequate amount, oxygen suppresses glycolysis. In intensive short term efforts oxygen supply lags behind cellular needs. Tissues are provided with the ability to derive energy from glycolysis during the short interval needed for additional oxygen to reach the front echelon.[72]

While studying the chemical changes in hypoxic cerebral tissues, Stone, Marshall and Nims (1941) observed an increase in lactic acid formation and phosphocreatine decomposition.[73] Three years later, Gurdjian, Stone and Webster (1944) reported that these chemical changes were proportional to the extent of oxygen want, occurred below critical levels of oxygen in inspired air and, within certain limits of severity and duration, were reversible on sufficient oxygenation of the brain.[74] Gellhorn (1941) became aware of the progressive increase in respiratory volume and blood pressure, both in human beings and in animals, when the oxygen concentration of inspired air is decreased. He interpreted these phenomena as evidence that the vasomotor mechanism and respiratory apparatus are excited by hypoxia, whereas other cerebral organs, including somatic centers, are depressed.[75]

CLINICOPATHOLOGIC CORRELATION

Brain Changes and Hypoxic Symptoms.—Himwich and Fazekas (1942, 1943) showed that arterial pressure of persons receiving metrazol® and electric shock therapy for mental disturbances is diminished, that prolonged treatment produces morphologic changes in the brain, that the degree of brain damage depends on the duration and severity of hypoxia and that resistance to oxygen want decreases with age.[76]

72. Dixon, K. C.: The Pasteur Effect and Its Mechanisms, Biol. Rev. Cambridge Philos. Soc. **12**:431 (Oct.) 1937. Burk, D.: The Pasteur Reaction: A Colloquial Consideration of the Pasteur and Neo-Pasteur Effects, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1939, vol. 7, p. 420. Johnson, M. J.: The Role of Aerobic Phosphorylation in the Pasteur Effect, Science **94**:200 (Aug. 29) 1941. Lipmann, F.: Pasteur Effect, in Symposium on Respiratory Enzymes, Madison, Wis., University of Wisconsin Press, 1942, pp. 48-73.

73. Stone, W. E.; Marshall, C., and Nims, L. F.: Chemical Changes in the Brain Produced by Injury and by Anoxia, Am. J. Physiol. **132**:770 (April) 1941.

74. Gurdjian, E. S.; Stone, W. E., and Webster, J. E.: Cerebral Metabolism in Hypoxia, Arch. Neurol. & Psychiat. **51**:472 (May) 1944.

75. Gellhorn, E.: Fundamental Principles in the Adjustment Reactions of the Organism to Anoxia, Ann. Int. Med. **14**:1518 (March) 1941.

76. Himwich, H. E., and Fazekas, J. F.: Factor of Hypoxia in the Shock Therapies of Schizophrenia, Arch. Neurol. & Psychiat. **47**:800 (May) 1942. Fazekas, J. F., and Himwich, H. E.: Anaerobic Survival of Adult Animals, Am. J. Physiol. **139**:366 (July) 1943.

Schnedorf, Lorhan and Orr (1941) reported 2 anesthetic deaths of surgical patients who sustained anoxic injuries to the brain identical in appearance to those in the brains of dogs subjected to the same anesthetic and surgical shock.[77] Horvath, Dill and Corwin (1943), while studying the effects of hypoxia on schizophrenic patients, observed this set of symptoms: cyanosis, drowsiness, increased perspiration, difficult breathing, restlessness, uncoordinated muscular movements, accumulation of saliva and mucus, retardation of cerebral response and eventual unconsciousness, with transient rigidity and clonic convulsions. On inhalation of room air, the patients recovered rapidly.[78] Barach (1944), comparing the symptoms of persons with acute arterial hypoxia to those of a person intoxicated with alcohol, spoke of elation and euphoria followed by drowsiness in some subjects, and initial drowsiness, mental dulness and irritability in others. He pointed out that patients with illnesses producing cerebral hypoxia have mental symptoms ranging from irrationality to coma when suddenly given inhalations of air rich in oxygen.[79] This toxic property of oxygen in high concentration and paradoxic anoxia were mentioned by Davy[80] and by Bert[81] and have been amply confirmed by others.[82] Blalock (1944) suggested that the brain may be able, in surgical shock, to extract more than its usual quota of oxygen from arterial blood—a possibility which may account for recoveries of apparently dead patients.[83]

In 1930, following similar accounts by German workers, Gildea and Cobb reported that temporary interference with cerebral circulation produces focal necrosis of the brain and that the earliest observable changes are enlargement of perineuronal spaces, moderate shrinkage of nerve cells, degenerative changes of the interstitium, dilatation of

77. Schnedorf, J. G.; Lorhan, P. H., and Orr, T. G.: Problem of Anoxia in Surgery and Anesthesia: Report of Experimental and Clinical Cases and Review of Literature, Arch. Surg. **43**:169 (Aug.) 1941.

78. Horvath, S. M.; Dill, D. B., and Corwin, W.: Effects on Man of Severe Oxygen Lack, Am. J. Physiol. **138**:659 (March) 1943.

79. Barach, A. L.: Impairment in Emotional Control Produced Both by Lowering and Raising Oxygen Pressure in the Atmosphere (A Fundamental Relation Between Psychic and Somatic Processes), M. Clin. North America **28**:704 (May) 1944.

80. Davy,[34] p. 197.

81. Bert,[41b] p. 740-749.

82. Behnke, A. R.; Forbes, H. S., and Motley, E. P.: Circulatory and Visual Effects of Oxygen at Three Atmospheres Pressure, Am. J. Physiol. **114**:436 (Jan.) 1936. Stadie, W. C.; Riggs, B. C., and Haugaard, H.: Oxygen Poisoning, Am. J. M. Sc. **207**:84 (Jan.) 1944.

83. Blalock, A.: Utilization of Oxygen by the Brain in Traumatic Shock, Arch. Surg. **49**:167 (Sept.) 1944.

blood vessels with perivascular necrosis and confluence of small foci to form larger lesions.[84]

Courville (1936, 1939) drew attention, as had many persons since Stanley in 1842, to asphyxia as a consequence of nitrous oxide anesthesia, pointed out the unique distribution of lesions and suggested the existence of an accessory vascular factor in the production of asphyxial necrosis.[85]

In 1939, van der Molen reported on the cortical cell changes occurring in the brains of aviators who had died from hypoxia encountered at an altitude of 28,000 feet.[86] Thorner and Lewy (1940) studied the histopathologic effects of repeated anoxia on the brains of cats and guinea pigs and observed that tissues of ectodermal and mesodermal origins are affected alike. These authors reasoned that a primary factor caused changes, possibly reversible, in cellular chemistry, evidenced by inability of neuronal cytoplasm to take basic stains, such as cresyl violet, and also appeared responsible for perivascular hemorrhage and coagulation, irreversible reactions, which destroyed minute portions of brain tissue. Integration of these two factors led to structural and permanent lesions of nerve cells and neuroglia. The effects of repeated hypoxia were cumulative; the lesions were irregular in distribution, and mental symptoms resulted comparable to those of a punch-drunk boxer. A single sixty second period of suffocation left traces of morphologic alteration in neurons and glial cells.[87]

Gross Lesions.—Schwartz [88] and others called attention to the late changes of anoxia in the brains of children who had survived asphyxia neonatorum. In such children there were diffuse degeneration of nerve cells, focal laminar necrosis of gray matter, focal cortical atrophy (microgyria), lobar sclerosis, hemispheric atrophy ("agenesia"), dif-

84. Gildea, E. F., and Cobb, S.: Effects of Anemia on Cerebral Cortex of Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

85. Courville, C. B.: Asphyxia as Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936; Pathogenesis of Necrosis of Cerebral Grey Matter Following Nitrous Oxide Anesthesia, Ann. Surg. **107**:371 (March) 1938; Untoward Effects of Nitrous Oxide Anesthesia with Particular Reference to Residual Neurologic and Psychiatric Manifestations, Mountain View, Calif., Pacific Press Publishing Association, 1939.

86. van der Molen, H. R.: Question of Sequels of Narcosis or of Asphyxia: Experimental Studies on Effect of Nitrous Oxide and of Oxygen Withdrawal on the Central Nervous System, Nederl. tijdschr. v. geneesk. **83**:4921 (Oct. 14) 1939.

87. Thorner, M. W., and Lewy, F. H.: Effects of Repeated Anoxia on the Brain: Histopathologic Study, J. A. M. A. **115**:1595 (Nov. 9) 1940.

88. Schwartz, P.: Erkrankungun des Zentralnervensystems nach traumatischer Geburtsschädigung: Anatomische Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:263, 1924.

fuse atrophy and brain cysts, some of which were of the porencephalous type.[89] These lesions, formerly thought to be due to imperfect morphogenesis or to trauma at birth and seen in spastic, ataxic, athetoid, epileptic and feebleminded children, were considered to be the residuals of prolonged acute or subacute anoxia.[90]

Lucas (1946) pointed out the cumulative effects of repeated or constant hypoxemia which, if prolonged, can cause damage varying from injury to a few nerve cells with slight mental aberration to massive cerebral necrosis and death.[91]

Titrud and Haymaker (1947) stated that aviators who collapsed as a result of short but sudden and severe deprivation of oxygen either died within a few minutes or hours or recovered completely. In those men who survived forty hours and then died, the cerebral lesions were essentially degeneration of myelin, especially in the internal capsule, and necrosis of nerve cells observed as gross pallor in stained sections of cerebral cortex (chiefly laminas III and IV), the striatum, cerebellum, hippocampus and anterior horns of the spinal cord.[92]

Microscopic Lesions.—Dellaporta (1939) reported the absence of demonstrable alterations in nerve cells in the brains of animals suddenly killed by complete withdrawal of oxygen. A survival period seemed necessary in order for the changes caused by pure anoxia to become histologically apparent.[93]

Morrison (1946) stated that the microscopic lesions of cortical gray matter, especially the frontal region, varied in distribution and from one animal to the other, but were qualitatively the same. Cortical nerve cells, showing "acute" injuries, were pale and swollen with eccentration of nuclei, granulation of tigroid substance and vacuolation of cytoplasm. Glial cells displayed similar changes and were reduced

89. Friedman, A. P., and Courville, C. B.: Atrophic Lobar Sclerosis of Early Childhood (Ulegyria): Report of Two Verified Cases with Particular Reference to Their Asphyxial Etiology, Bull. Los Angeles Neurol. Soc. **6**:32 (March) 1941.

90. Courville, C. B., and Marsh, C.: Neonatal Asphyxia: Its Encephalic Residuals and Mechanism of Their Production, Bull. Los Angeles Neurol. Soc. **9**:121 (Sept.-Dec.) 1944. Courville, C. B.: Pathology of the Central Nervous System, ed. 2, Mountain View, Calif., Pacific Press Publishing Association, 1947, pp. 89, 436-439; Cerebral Anoxia and Its Residuals, M. Arts & Sciences **1**:16 (April); 35 (July) and 68 (Oct.) 1947; **2**:67 (April) 1948.

91. Lucas, G. B.: Anoxia and the Central Nervous System: An Experimental and Clinical Study, Thorax **1**:128 (June) 1946.

92. Titrud, L. A., and Haymaker, W.: Cerebral Anoxia from High Altitude Asphyxiation, Arch. Neurol. & Psychiat. **57**:397 (April) 1947.

93. Dellaporta, A. N.: Die Veränderungen des Zentralnervensystems nach Luftverdrünnung und nach Hunger, Beitr. z. path. Anat. u. z. allg. Path. **102**:268, 1939.

in number. Neurofibrillae remained intact at first. Subcortical nerve cells, exhibiting "subacute" or "chronic" changes, were darkly stained and shrunken with elongated bodies, hyperchromatic processes, pyknotic perikarya and tortuous apical dendrites. Some cells showed satellitosis; some were mildly pallid; others were ghostlike. Oligodendroglia were increased in number, and capillary hyperplasia was pronounced. Prolonged hypoxia caused proliferation of microglia, gitter cell formation, perivascular cuffing with hematogenous cells and disappearance of neuronal bodies through either lysis or neuronophagia. Lesions of the white matter, mostly in subcortical regions, consisted of some myelin degeneration (probably secondary to necrosis of nerve bodies [94]), hyperplasia of microglial and endothelial cells, oligodendrogliosis along capillaries and neurofibrillary swelling. All four types of anoxia produced lesions identical in appearance.[95]

Asphyxia and Morbus Caeruleus.—It is unfortunate that the brain was not examined in the case of Henry F. Gilbert, illustrious American musical composer, who lived for sixty years with the *maladie bleue* due to the tetralogy of Fallot.[96] In describing the cerebral lesions of a 17 year old youth who died of congenital heart disease complicated by subacute bacterial endocarditis, Scholz (1941) showed photographs which fit previous descriptions of anoxic cerebral changes from other causes.[97]

Although woven with strong threads of scientific thought—leading from origins diverse in time and place—the fabric of knowledge pertaining to asphyxia is notoriously incomplete, albeit fine in texture, and serves little more than a diaphanous covering for present ignorance. With hope of some gain, therefore, I shall describe experiments of nature in the cases of 3 infants with cardiac anomalies who died because of uncomplicated oxygen deficiency in various degrees of severity and duration.

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94. Windle, W. F.; Becker, R. F., and Weil, A.: Alterations in Brain Structure After Asphyxiation at Birth, J. Neuropath. & Exper. Neurol. **3**:224 (July) 1944.

95. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

96. Kurtz, C. M.; Sprague, H. B., and White, P. D.: Congenital Heart Disease: Interventricular Septal Defect with Associated Anomalies in Series of Three Cases Examined Postmortem, and Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of Fingers, Am. Heart J. **3**:77 (Oct.) 1927. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot: Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, J. A. M. A. **92**:787 (March 9) 1929.

97. Scholz, W.: Ueber den Einfluss chronischen Sauerstoffmangels auf das menschliche Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:426, 1941.

REPORT OF CASES

CASE 1.—A 3 year old white girl was admitted to the Colorado General Hospital, Dec. 8, 1947, for study and treatment of congenital heart disease. The mother, otherwise apparently healthy, was said to have had rubella during her third month of pregnancy with this child. Delivered normally at full term, the infant had a heart murmur, anemia and bilateral cataracts. During the first year of life she recovered from an illness diagnosed as rheumatic fever; during the second year she was treated for pneumonia. Three operations on the eyes were

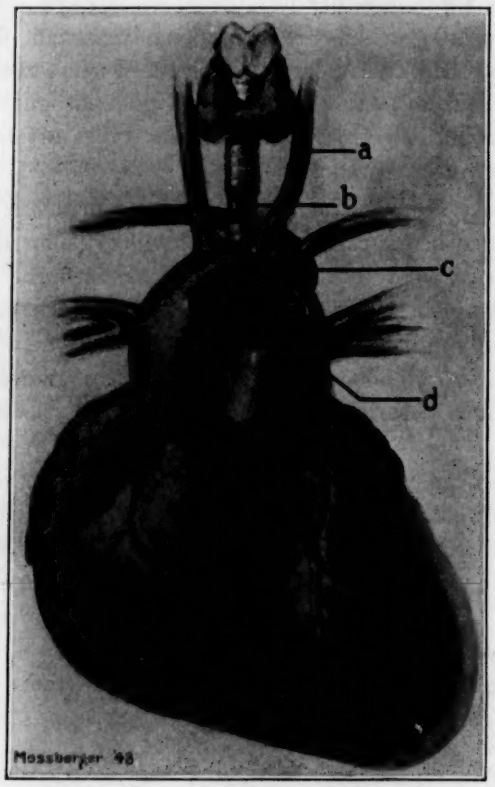

Fig. 1.—Drawing of heart and great vessels (case 1): *a*, left common carotid artery; *b*, esophagus; *c*, aberrant right subclavian artery passing between trachea and esophagus, and *d*, patent ductus arteriosus.

attended with some degree of success. The girl was well nourished and fairly well developed and had no cyanosis or jaundice. She had pigeon-breast deformity, bilateral strabismus, more pronounced on the right, and bilateral nystagmus with the slow component to the right. The child spoke in an unintelligible mumble; psychometric evaluation placed her on a mentally defective level. Harsh systolic murmurs and a thrill were most pronounced in the left second intercostal space; a soft systolic and diastolic souffle was audible over the cardiac apex. The blood pressure in the right arm was 100 systolic and 60 diastolic, in the left arm 130 systolic and 60 diastolic. Roentgenograms of the chest showed enlargement

of the heart to the left, with prominence of the contour of the pulmonary artery and an esophageal constriction slightly above the level of the aortic arch. Electrocardiograms and clinical laboratory tests revealed nothing significant.

During an exploratory thoracotomy two weeks after her admission to the hospital, the child's patent ductus arteriosus was ligated and an aberrant right subclavian artery was tied and divided. The general condition of the patient during operation and immediately thereafter was good. En route to the ward the girl's breathing and pulse stopped. Back in the operating room it was found that the ligature had slipped off the proximal end of the right subclavian artery and the left pleural cavity was filled with blood. The arterial stub was immediately clamped and tied; the heart was massaged, and 400 cc. of citrated blood was transfused. In twelve minutes cardiac pulsation began; color returned to the skin, and gasping respiratory movements were made. With 300,000 units of penicillin in the pleural space and a drain leading therefrom, the thoractomy wound was again closed. Four hours afterward the patient was comatose and spastic, although her respiration was regular and her blood pressure was 120 systolic and 80 diastolic. During the last ten hours, her systolic pressure fell to 90; her breathing became progressively more hyperpneic; she remained comatose and died fifteen hours after resuscitation.

Observations at Autopsy.—The left pleural cavity was brimful of thin, bloody fluid surrounding the collapsed left lung. The pericardial sac appeared normal. The heart, somewhat bulbous and weighing 100 Gm., was normal in musculature, vascularity and valvular circumferences. There was a narrow patent slit 2 cm. along the anterior margin of the fossa ovalis. The patent ductus arteriosus was 1 cm. long and 1 cm. in diameter. The aorta, normal in circumferences throughout, gave rise to four main trunks. The absent innominate artery was replaced at its usual site by the right common carotid artery. The left common carotid and left subclavian arteries arose from their usual origins. The right subclavian artery came from the superoposterior part of the left end of the aortic arch and passed to the right side between the trachea and esophagus (fig. 1). The brain (embalmed before examination) weighed 1,100 Gm. and presented no gross abnormality. The other organs were not remarkable.

Microscopic Examination.—The myocardial fibers were larger than normal. Otherwise, all structures of the heart, aorta and great vessels were not unusual. The left lung showed complete or partial collapse of alveoli, some of which contained proteinaceous fluid and a little blood. Nuclear regions in all parts of the central nervous system, especially the frontal cortex and globus pallidus, took the cresyl violet stain poorly. This staining property was not diffuse but appeared as the fusion of large patches of pallor. Nerve cells in general were swollen and pale with eccentric nuclei, powdered or absent tigroid substance, swollen dendrites and fragmented nucleoli. Some cells appeared like the finely reticulated ghosts of former neuronal bodies (fig. 8 *c*). In the basal ganglions especially were occasional shriveled nerve cells with darkly stained nuclei, clumped cytoplasmic chromatin and thin, tortuous apical dendrites (figs. 2, 3 and 4). Glial cells generally were very pale. Perivascular hemorrhage or cuffing with hematogenous cells, neuronophagia, satellitosis and oligodendrogliosis were not observed.

Comment.—Many of the persons in whom the number of branches of the adult aortic arch is increased to four show the right subclavian

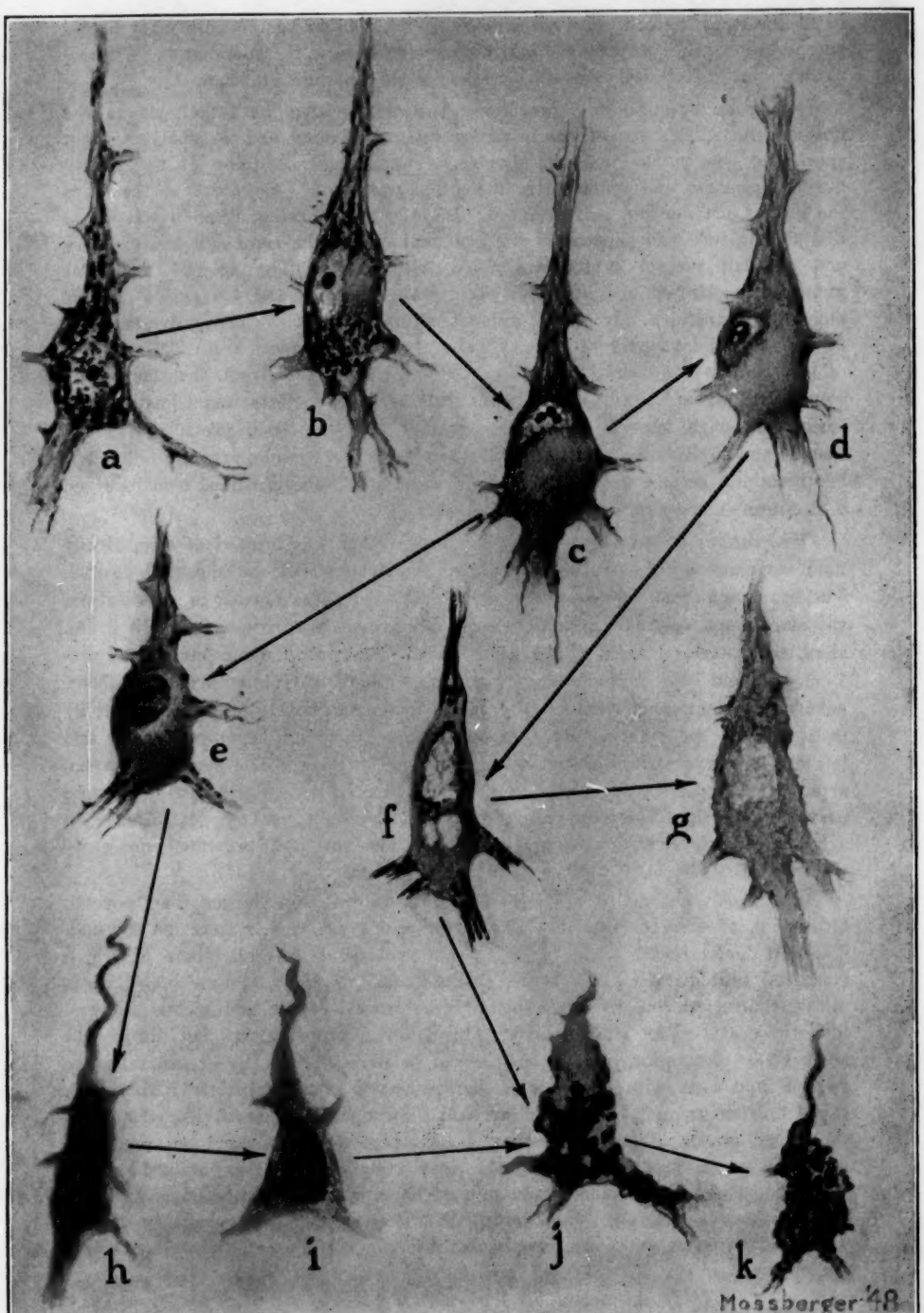

Figure 2

(See legend on opposite page)

artery arising from the left end of the arch. This is probably due to the fact that the right fourth aortic arch of the embryo becomes the proximal part of the right subclavian artery and the left fourth embryonic arch persists as the arch of the adult aorta. Thus, both the embryonal third aortic arches, which later become the common carotids, may develop directly from points on the aortic sac anterior and proximal to the right subclavian artery.[98] In crossing to the right side, this artery may compress the esophagus to cause dysphagia lusoria and may, in turn, be compressed to cause decreased pressure in the distal part of the artery.

In this patient, massive hemothorax from the surgically divided right subclavian artery produced sufficient cerebral hypoxia, both from loss of blood and collapse of the lung to cause paralysis of cardiac and respiratory mechanisms. Although these functions resumed after appropriate emergency measures, lack of oxygen was either too severe or too long (or possibly both) for cellular activity to continue permanently. Loss of staining properties and swelling of nerve cell bodies probably represent the first effects of cerebral anoxia. Those nerve cells showing shrinkage could possibly be the results of former asphyxia, either at birth or during the respiratory illness, and might conceivably account for the neurologic manifestations and mental retardation. In this connection, it may be mentioned that some nerve cells in various nuclear regions — Clarke's columns of the spinal cord, gracilis and cuneate

98. (*a*) Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 24, Philadelphia, Lea & Febiger, 1942, p. 576. (*b*) Patten, B. M.: Human Embryology, Philadelphia, The Blakiston Company, 1946, p. 624.

Fig. 2.—Drawing of nerve cells from the frontal cortex, showing anoxic changes in approximate "chronologic" sequence: *a*, normal-appearing neuronal body (case 2), with large cytoplasmic granules, centrally placed and finely reticulated unstained nucleus and round, darkly stained nucleolus; *b*, "early" "acute" change (case 1), with swelling of apical dendrite, powdering of cytoplasmic granules, paranuclear pallor and eccentration of nucleus; *c*, further advanced "acute" change (case 1), with swelling of the cell body, disappearance of most of the cytoplasmic granules and fragmentation of nucleolus; *d*, late "acute" change (case 1), with pronounced swelling of the apical dendrite and cell body, complete disappearance of cytoplasmic granules, vacuolation of nucleolus; *e*, "subacute" change (case 2), with swelling of the apical dendrite and cell body, disappearance of cytoplasmic granules, darkly stained nucleus and fragmentation of nucleolus; *f*, "subacute" change (case 2), with some shrinkage of the cell body, clumping of chromatin in cell processes, vacuolation of cytoplasm, absence of tigroid granules, rhexis of nuclear membrane and disappearance of nucleolus; *g*, necrosis (ghost cell, cases 1 and 2), with fine stippling of the remains of the former neuronal body; *h*, "chronic" change (case 3), with shrinkage of the darkly stained cell body, shrinkage and tortuosity of apical dendrite and shrinkage and clumping of the darkly stained nuclear chromatin; *i*, "chronic" change (case 3), with pallor of cytoplasm of the cell body and its processes and central clumping of all chromatin material; *j*, "chronic" change (case 3), with variegated vacuolation of cytoplasm and clumping of chromatin and disruption of entire cellular structure, and *k*, "chronic" change (case 3), with shrinkage of cell body and its processes, clumping of chromatin material and encrustation with darkly stained granules (calcium and iron salts).

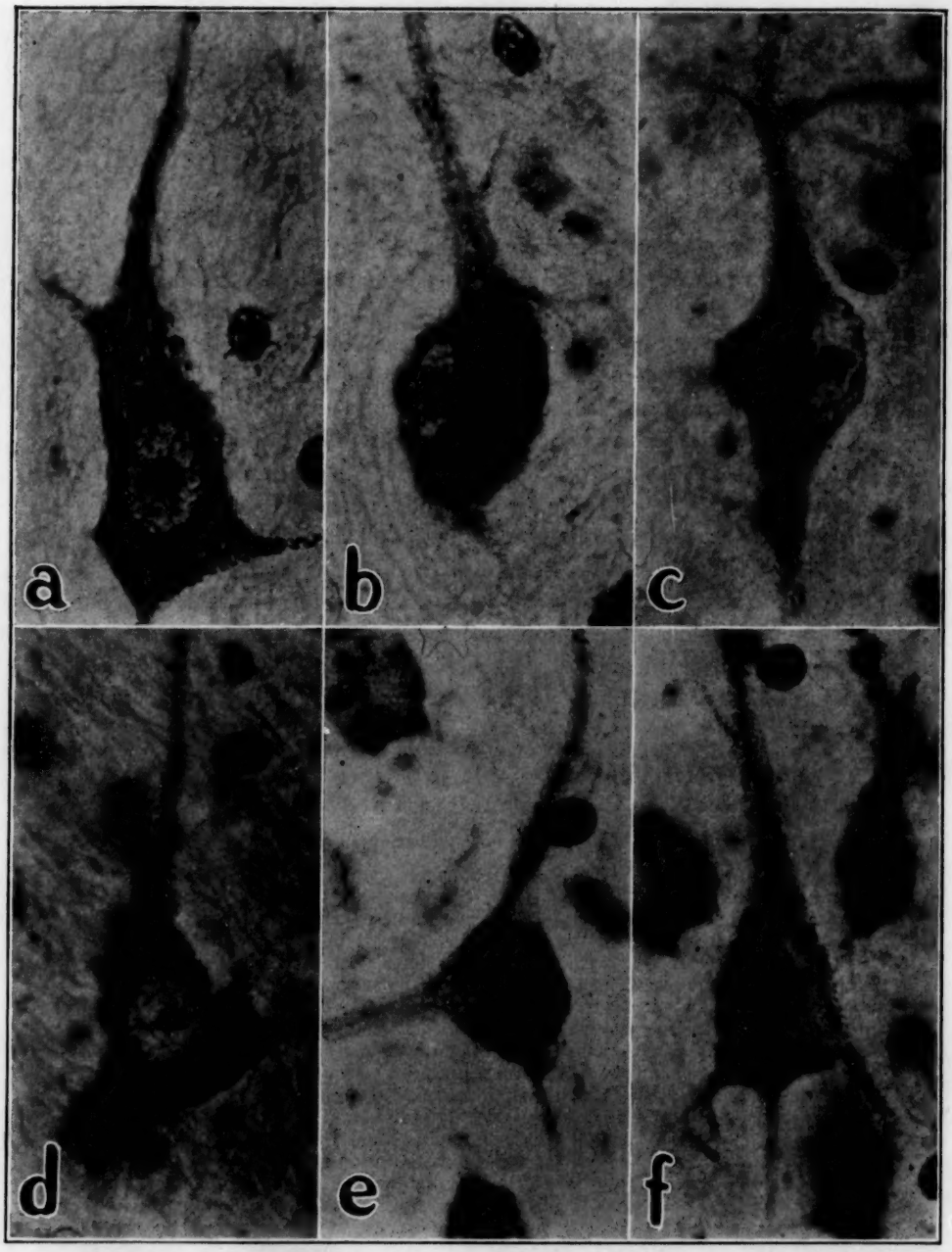

Fig. 3.—Photomicrographs of neuronal bodies from frontal cortex: *a*, normal-appearing nerve cell (case 2); Nissl stain; × 910; *b*, "acute" nerve cell change (case 1), corresponding to drawing 2 *b;* Nissl stain; × 910; *c*, "acute" nerve cell change (case 1), corresponding to drawing 2 *c*; Nissl stain; × 910; *d*, "acute-subacute" nerve cell change (case 2), corresponding to drawings 2 *d* to *f*; Nissl stain; × 910; *e*, "acute-subacute" nerve cell change (case 2), corresponding to drawings 2 *d* and *e*; Nissl stain; × 910, and *f*, "subacute" nerve cell change (case 2), corresponding to drawing 2 *e;* Nissl stain; × 910.

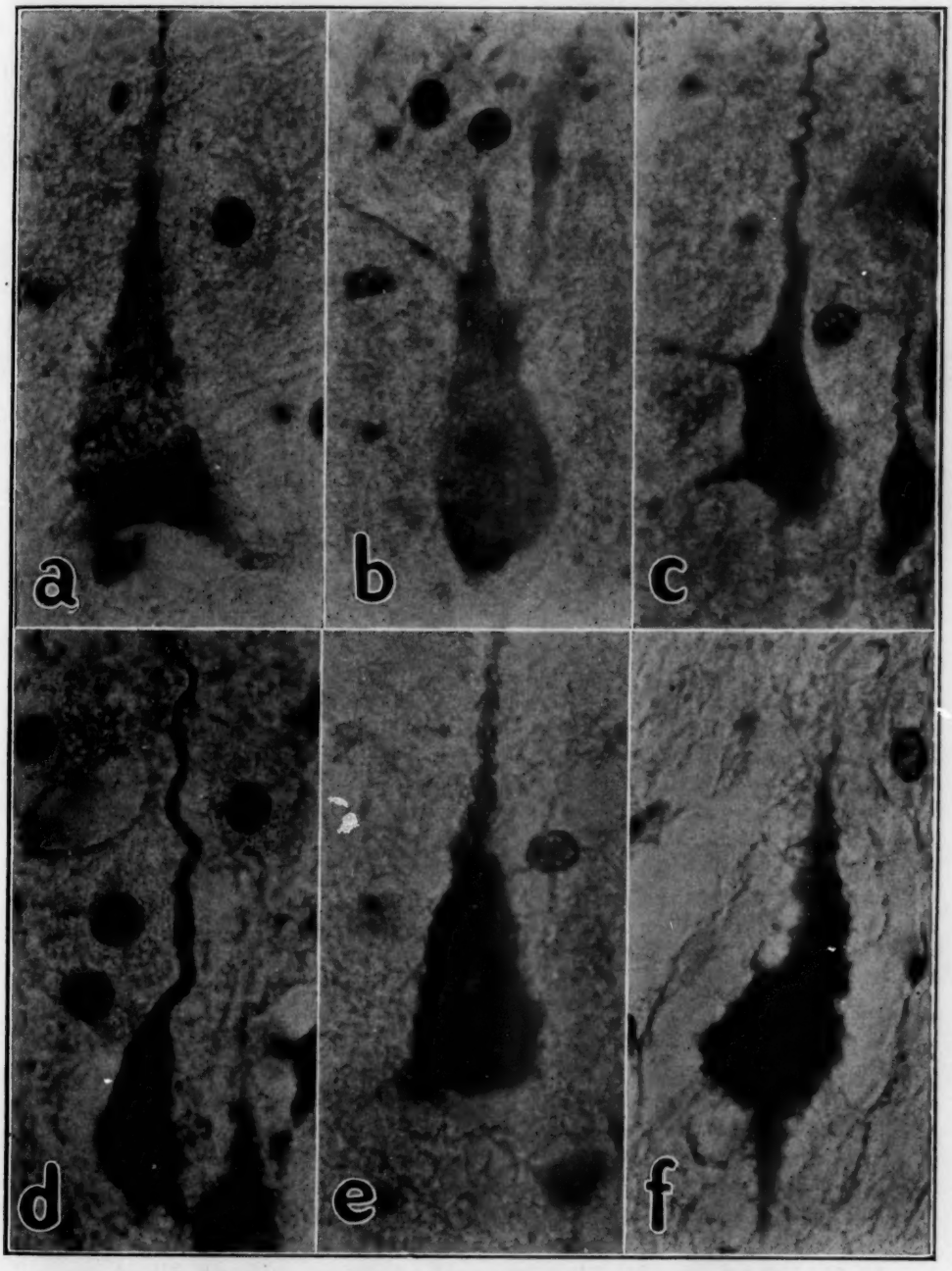

Fig. 4.—Photomicrographs of neuronal bodies from frontal cortex: *a*, "subacute" nerve cell change (case 3), corresponding to drawings 2 *f* and *g*; Nissl stain; × 910; *b*, necrosis of nerve cell (case 1), corresponding to drawing 2 *g*; Nissl stain; × 910; *c*, "chronic" nerve cell change (case 3), corresponding to drawing 2 *i*; Nissl stain; × 910; "chronic" nerve cell change (case 3), corresponding to drawing 2 *h*; Nissl stain; × 910; *e*, "chronic" nerve cell change (case 3), corresponding to drawings 2 *f* to *j*; Nissl stain; × 910, and *f*, "chronic" nerve cell change (case 3) corresponding to drawing 2 *k*; Nissl stain; × 910.

nuclei, raphe of the medulla oblongata, reticular formation of the pons and mesencephalic nucleus of the fifth cranial nerve—normally show central pallor and eccentric nuclei. In older persons, without manifestation of neurologic disease during life, some of the anterior horn cells and neuronal bodies in the deeper laminas of the cerebral cortex may be shrunken and stained darkly to resemble chronically degenerated cells.[99]

CASE 2.—A full term white male infant was born in the Colorado General Hospital, Feb. 18, 1948. He cried feebly and nursed poorly. Cyanosis, present at birth, progressed in intensity, especially over the head and extremities; breathing became difficult and grunting in character; the skin became cold, clammy and somewhat leathery. All supportive measures failed, and the child died forty-six hours after delivery.

Observations at Autopsy.—Clear, straw-colored fluid filled the pericardial sac. The bulbous heart, weighing 30 Gm., had a flabby hyperemic ventricular wall, averaging 3 mm. in thickness. The right auricle was distended with blood; the left was remarkably small. The dilated main pulmonary trunk (3.5 cm. in circumference) seemed to continue as the descending aorta through the ductus arteriosus, which was 1.5 cm. long and 3 cm. in circumference. The extremely small left ventricle (6 mm. long, 3 mm. in diameter) appeared like a blind pouch in the thick left side of the ventricular wall. The mitral valvular cusps and papillary muscles were minute but well developed. There was no aortic orifice. The very small aortic valves were fused along their apposing margins. The patent coronary ostiums and arteries were in their usual positions. The first portion of the aorta was atretic (2 mm. in circumference) and directed in a straight line obliquely upward behind the pulmonary artery to its junction with the descending portion at the distal end of the ductus. The smooth, red epicardium showed severe vascular congestion but normal distribution of adipose tissue. The foramen ovale was 10 mm. in diameter and widely patent (fig. 5). The unembalmed brain, weighing 390 Gm. and normal in external configuration, showed leptomeningeal vascular engorgement and congestion of blood vessels throughout the cerebrum, cerebellum, pons and medulla but no grossly apparent hemorrhage. The dark, purple-red choroid plexus was stuffed with blood, and the normal-sized cerebral ventricles contained sanguineous fluid. Fibers of the falx cerebri and tentorium cerebelli were intact, although vessels between these dural reduplications bulged with blood. Intracranial birth injuries or anomalies could not be demonstrated. Other organs, including the lungs, were intensely hyperemic.

Microscopic Examination.—All blood channels of the heart wall, the lungs, kidneys, liver and spleen were highly congested. Striations of myocardial fibers were not visible. Fibrous tissue was abundant in and around the wall of the aortic conus. Alveolar edema and hemorrhage characterized the lungs throughout. The splenic pulp contained "pools" of blood which obscured the architecture of pulp cords. The pericentral liver cells were pale, vacuolated, pyknotic and distorted by blood-dilated sinusoids. Leptomeningeal vessels and all capillaries of the cerebral substance were intensely congested with blood. Hemorrhage or vascular proliferation was not observed. Perivascular and perineuronal spaces did not

99. Weil, A.: Textbook of Neuropathology, ed. 2, New York, Grune & Stratton, Inc., 1945, pp. 15-23.

appear enlarged. Glial cell hyperplasia was mild and generalized; however, oligodendrogliosis along capillaries was nowhere apparent. Nerve cell bodies in all nuclear regions showed changes ranging from the "acute" type, with swelling, pallor and loss of staining properties to the "chronic" type, with shrinkage and clumping of darkly stained chromatin material. In lamina V of the cerebral cortex, large Betz cells with "ischemic" shrinkage were occasionally lying beside those with "edematous" swelling. The majority of neurons were approximately normal in size, contained no cytoplasmic granules and presented darkly stained nuclei and irregularly shaped or fragmented nucleoli (fig. 2 *d* and *e*, 3 *e* and *f*).

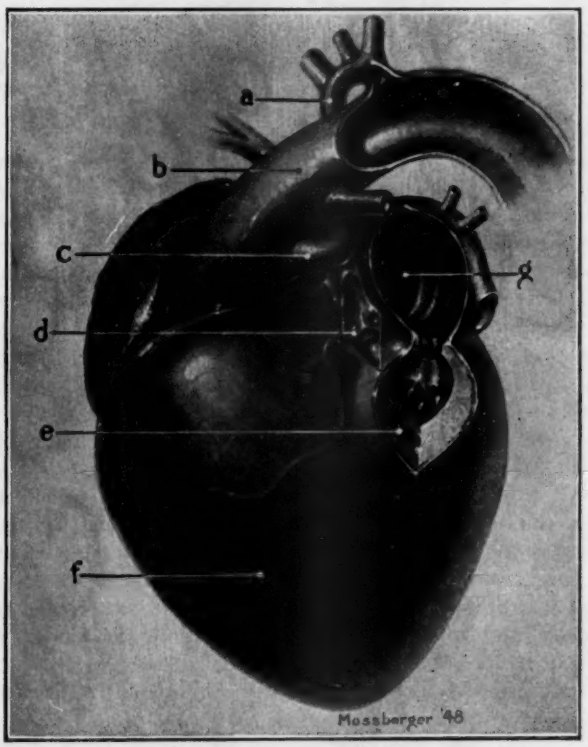

Fig. 5.—Drawing of heart and great vessels (case 2): *a*, arch of atretic aorta; *b*, ductus arteriosus; *c*, right pulmonary artery; *d*, fused aortic cusps; patent coronary ostia; *e*, hypoplastic left ventricle; *f*, hugely dilated right ventricle, and *g*, foramen ovale.

Comment.—Maude Abbott collected 12 similar cases described as truncus solitarius pulmonalis, with hypoplasia of the mitral orifice and left ventricle,[100] and attributed the condition to fetal myocarditis with scarring of the conus walls just below the aortic cusps.[101] In this patient,

100. Abbott, M.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, pp. 48 and 49.

101. von Zalka, E.: Histologische Untersuchungun des Myokards bei kongenitalen Herzveränderungen, Frankfurt. Ztschr. f. Path. **30**:144, 1924.

retrograde circulation of blood from the left auricle through the foramen ovale—thence to the small aortic arch via the right auricle and ventricle, pulmonary artery and ductus arteriosus—provided sufficient cerebral oxygenation to sustain postuterine life for two days. Whether or not some hypoxia existed prior to birth is a moot question.

The presence of cells with "chronic" changes lying alongside those with "acute" changes upsets any correlation of time with histologic appearance, unless one considers individual cellular resistance to hypoxia, variations throughout the brain in the severity of hypoxia and focal concentration of the factors accessory to hypoxia. Thus, it may be the part of wisdom to designate a diseased neuron with its various changes by a descriptive morphologic term without implying the age of the process or the condition which produced it.

CASE 3.—A 5 month old male infant entered the Colorado General Hospital, Dec. 6, 1947, with intense cyanosis, respiratory difficulty and a strident cough. Born at full term, the child did well and appeared normal for six weeks. At this time the mother noticed occasional cough and a transient bluish discoloration of the upper part of the body. At 3 months of age the cough had become more frequent and severe and was accompanied with difficulty in breathing. By the time of his admission to the hospital, the cough was crouplike, the breathing rapid and wheezy and the cyanosis permanent. The baby presented duskiness and coolness of the skin of the head, neck, shoulders, chest and upper extremities. The back, buttocks, abdomen and lower extremities were pink and warm (fig. 6). Respirations were rapid and labored. Clinical evidence of pneumonia was not elicited. The pharynx was injected, and tenacious mucus clung to its lining. The heart rate varied from 130 to 160 per minute. A harsh systolic murmur was easily heard over the entire precordium. Roentgenograms and fluoroscopy showed moderate enlargement of the heart to the left, widening of the mediastinum at the base of the heart, enlargement of both ventricles and some displacement of the trachea at the level of the aortic arch. Except for sinus tachycardia, electrocardiographic tracings were within normal limits. Clinical laboratory examinations revealed nothing significant. In spite of continuous oxygen inhalation, pharyngeal aspiration, digitalization and other supportive measures, the child's clinical course was steadily downward, and he died one month after his admission to the hospital.

Observations at Autopsy.—The boy's body was well developed and proportioned. The heart, normal in shape and weighing 60 Gm., extended to the left costal border. The epicardium was smooth and showed normal vascularity and distribution of adipose tissue. The right ventricular wall measured 8 to 11 mm. in thickness; the left, 8 to 13 mm. Circumferences of the valves were: tricuspid, 5 cm.; pulmonary, 4 cm.; mitral, 4 cm., and aortic, 2 cm. The endocardium, valve cusps, papillary muscles and chordae tendineae appeared normal grossly. Coronary orifices and arteries were patent. The fossa ovalis had webbed margins and admitted a fine probe diagonally through its anterior margin. The ductus arteriosus, 1.5 cm. long, 1.8 cm. in diameter, appeared like the continuation of the pulmonary artery into the descending aorta. The aorta arose from the right ventricle and showed, immediately beyond the origin of the great vessels of the neck, a narrow coarctation 1 cm. long with a distal orifice that barely admitted a fine probe. Circumferences of the aorta were: ascending portion, 2.2 cm.;

arched portion, 2.5 cm.; coarctation (distal orifice), 0.2 cm.; descending thoracic portion, 2.0 cm., and abdominal portion, 1.8 cm. The upper part of the ventricular septum presented a circular opening, 1 cm. in diameter, which was bounded throughout the lower half of its circumference by the smooth rounded margin of the septal muscle. The pulmonary artery arose directly above this interventricular foramen with approximately half of its ostial circumference on each side of the septum. Projecting downward from the right side of the pulmonary artery was a thick, smooth elliptic band of muscle which practically occluded the septal defect on the right side. The widely patent ductus arteriosus connected with the aorta

Fig. 6.—Drawing of baby (case 3), showing cyanosis of the head, neck, shoulders, chest and upper extremities.

just below the coarctation previously described (fig. 7). All veins appeared normal. The lungs were yellowish pink and fully inflated. The embalmed brain, weighing 640 Gm., showed normal external configuration and cut-surface markings throughout. The symmetric cerebral ventricles were normal in size and contained a small quantity of clear, watery fluid.

Microscopic Examination.—Although normal in size and nucleation, the myocardial fibers showed no striations and appeared like elongated clumps of reddish brown granules surrounded by the fiber sheaths. All structures of the lungs appeared normal. The myeloid-erythroid ratio of myelogenous cells in vertebral

marrow was approximately 1. A great many of the neuronal bodies of the cerebral cortex, basal ganglions, cerebellum, pons, medulla and upper part of the cervical portion of the spinal cord showed morphologic changes like those of "chronically degenerated" cells (fig. 8 *d*). A few cells showed cytoplasmic swell-

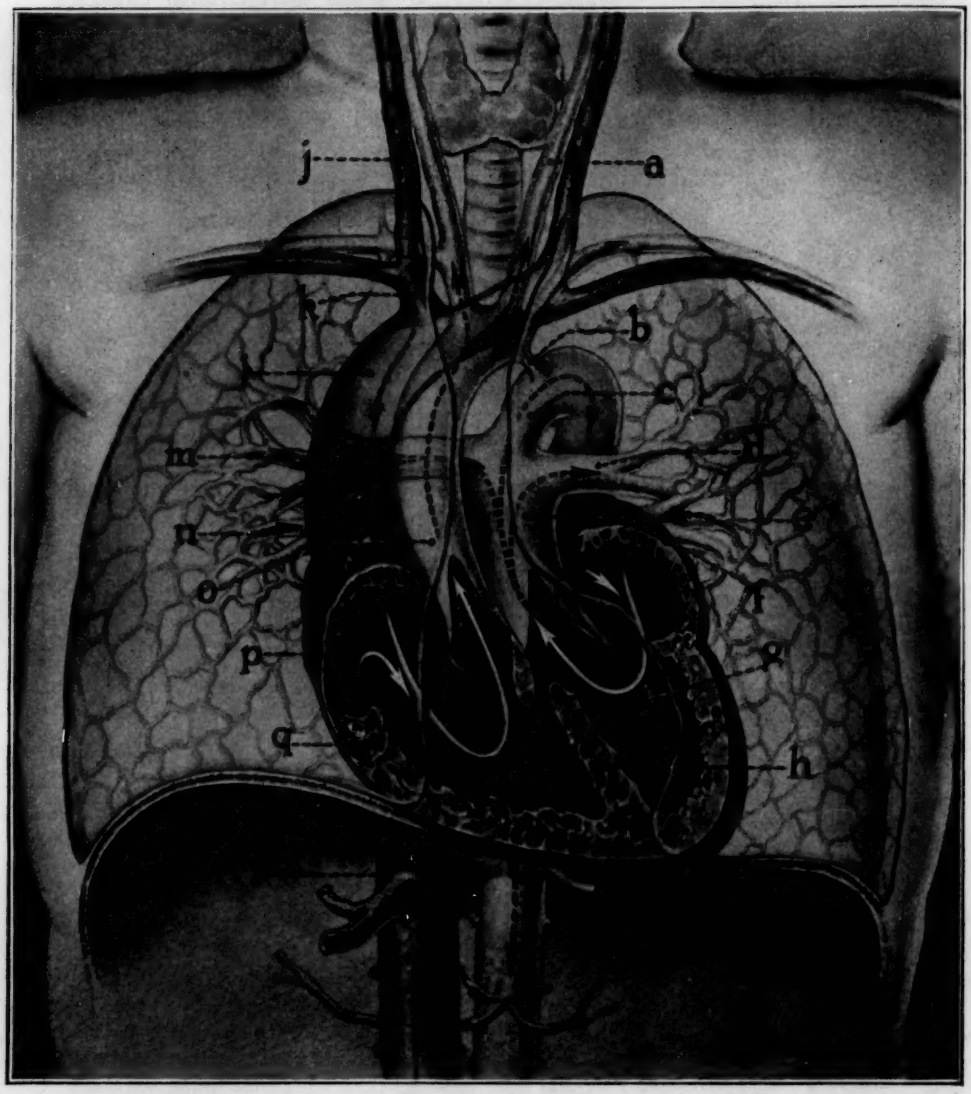

Fig. 7.—Drawing of cardiopulmonary circulation (case 3): *a*, left common carotid artery; *b*, coarctation of aorta; *c*, widely patent ductus arteriosus; *d*, left pulmonary artery; *e*, left pulmonary veins; *f*, pulmonary stem from left ventricle; *g*, proximal part of bulbar septum nearly closing defect of the ventricular septum; *h*, ventricular septum; *i*, descending aorta; *j*, right internal juglar vein; *k*, right innominate vein; *l*, superior vena cava; *m*, right pulmonary arteries; *n*, right pulmonary veins; *o*, ascending aorta from right ventricle; *p*, dilated right auricle; *q*, hypertrophied wall of right ventricle, and *r*, inferior vena cava.

ing, darkly stained nuclei and absence of central tigroid substance. Some cells showed clumping of "chromatin" material in the cytoplasm and its processes, nucleolar fragmentation, vacuolation or lysis and complete disappearance of tigroid substance. Many cells were shrunken, with rough, irregular outlines, and stained nearly black throughout without differentiation of cytoplasm, nucleus or nucleolus. Apical dendrites were thin and tortuous. With intense light shining through them, these shrunken cells appeared to be filled with rounded masses

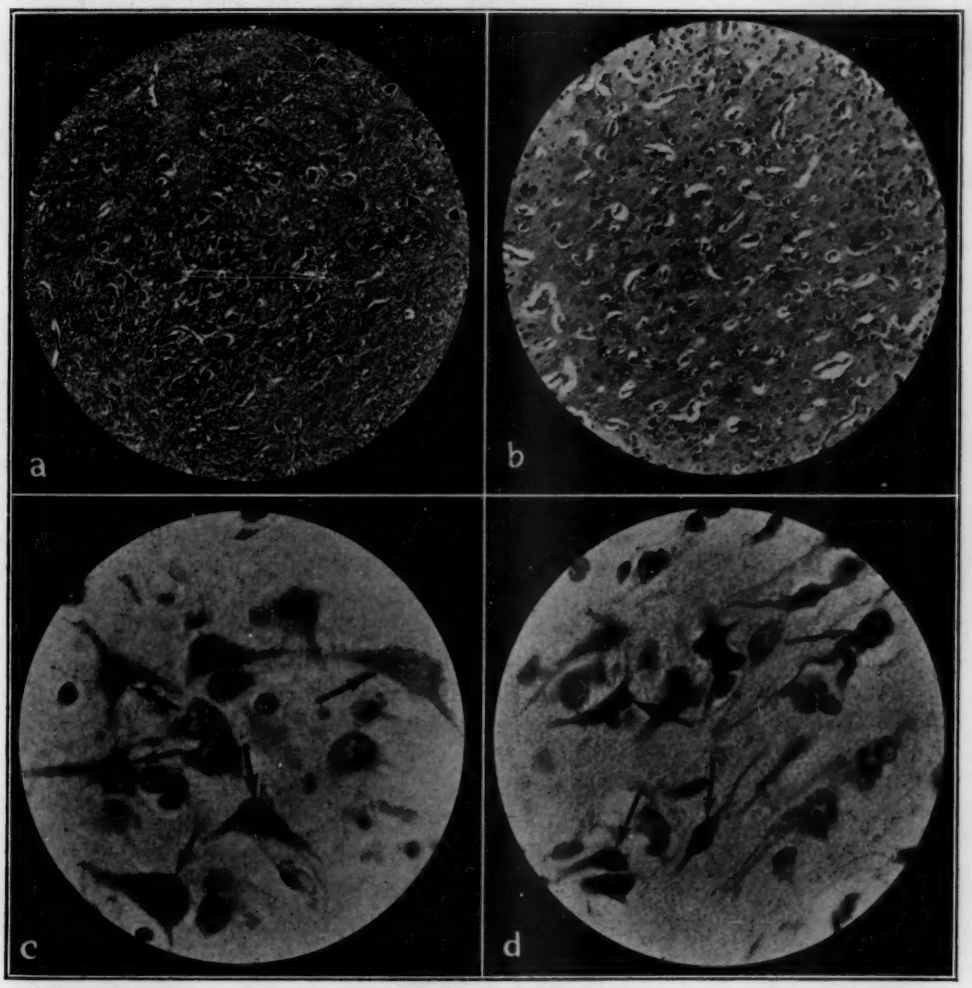

Fig. 8.—Photomicrographs: *a*, section through midportion of inferior olive (5 month old child who died of fulminating enteritis, cause unknown), showing normal distribution of nerve cells, glial cells and capillaries; hematoxylin and eosin stain; × 80 (this section is shown to compare with section *b*); *b*, section through midportion of inferior olive (case 3), showing absence of nerve cells, increased number of glial cells, capillary hyperplasia; hematoxylin and eosin stain; × 80; *c*, section through frontal cortex (case 1 showing "acute" changes of nerve cells; Nissl stain; × 355, and *d*, section through frontal cortex (case 3), showing "chronic" changes of nerve cells; Nissl stain; × 355.

of deeply stained chromatin (figs. 2 and 4). Except for a few isolated instances, neuronophagia, oligodendrogliosis and definite cell ferrugination (iron encrustation) were not observed. In all nuclear regions, especially the frontal cerebral cortex, globus pallidus and inferior olive of the medulla oblongata, there were pronounced capillary hyperplasia, glial cell proliferation and conspicuous scarcity of nerve cell bodies. In some places ganglion cells were absent altogether (fig. 8 *b*). Nothing remarkable was observed in other organs.

Comment. — The interventricular defect of this infant's heart occurred at the membranous portion of the septum due to improper union, at this point, of the connective tissue crest of the interventricular muscular ridge, the fused tubercles of the endocardial cushions and the conus prominences of the bulbar septum. In addition to failure of these developing structures to unite, the truncus and conus ridges failed to follow their normal spiral course to the crest of the ventricular septum. Thus, the aorta developed from the right ventricle, the pulmonary artery from the left. The interventricular septum remained open and the pulmonary artery became dilated, more as alleviating measures than as complications, in order that both ventricles might share the load of pumping blood into the aorta.[102]

Complicating and neutralizing the aforementioned compensations for developmental error was a second anomaly—severe coarctation—distal to which the widely patent ductus arteriosus entered the aorta. To increase the difficulty still further, the thick, muscular proximal part of the bulbar septum overlapped the interventricular foramen to prevent much oxygenated blood from entering the right ventricle. Consequently, most of the postpulmonary blood passed either back into the pulmonary system or through the ductus arteriosus into the descending aorta (fig. 7). As a result, the upper part of the child's body was in a constant state of oxygen want. The valvelike constriction at the distal end of the coarctation was apparently large enough during the first six weeks of life to admit enough arterial blood into the aortic arch to maintain adequate oxygenation of the head and upper extremities. This constriction either remained stationary in diameter, as other structures grew around it, or actually decreased in caliber, to result in insufficient oxygen supply to the upper part of the body. A description of a similar cardiac malformation could not be found in available medical literature.[103]

Mild erythroid hyperplasia in bone marrow and capillary proliferation in nuclear regions of the brain probably were attempts to maintain oxygenation of the brain by increasing the oxygen-carrying power of

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102. Patten, [98b] p. 679.

103. Moore, R. A.: A Textbook of Pathology: Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease, Philadelphia, W. B. Saunders Company, 1944, pp. 934-941. Abbott,[100] pp. 16-21; 32-33 and 56-57.

the blood and expanding the volume of the cerebral vascular bed. This compensation could not, however, forestall progressive anoxic degeneration of nerve cells to the point of functional failure of the respiratory center. These nerve cell changes no doubt represent the effects of uncomplicated and sustained cerebral hypoxia.

COMMENT

Because the incompressible brain is within a closed, unexpandable box, it follows that adequate cerebral oxygenation in case of hypoxemia must be maintained by an increased rate of blood flow through the brain.[104] Increase in arterial blood pressure, caused by hypoxic excitation of the vasoconstrictor mechanism, either directly or through the carotid reflex, speeds blood through the brain faster than the three seconds usually taken. Due to the asphyxial effect, leptomeningeal vessels dilate slightly to increase the total capacity of cerebral blood channels.[105] Nerve cells, intimately related to "through" (not "end") capillaries and at times even pierced by them,[106] are extremely sensitive to sudden variations in blood oxygen. This would suggest that efficient nerve cell metabolism practically requires neuronal inundation by oxygenated blood.

The respiratory quotient of the brain is practically unity. Glucose, present in brain tissue in about the same concentration as in blood, is the main substrate for respiration of gray matter and appears to be its main source of energy. Nuclear tissue oxidizes glucose with pyruvic acid as an intermediary step and, unlike nerve fibers, produces a small quantity of lactic acid. Under anaerobic conditions larger amounts are produced which may initiate the proteolytic processes responsible for alterations in structure and staining qualities of nerve cells.[107] Relationships of blood glucose to oxygen and of hypoglycemia to hypoxemia are similar and apparently supplemental.[108] Nerve tissue seems able to withstand periods of oxygen want (Pasteur effect) and temporarily to derive energy from glycolysis and the breakdown of

104. Best and Taylor, [89b] p. 289.

105. Howell, W. H.: Howell's Textbook of Physiology, ed. 15, edited by John F. Fulton, and others, Philadelphia, W. B. Saunders Company, 1946, pp. 923 and 924.

106. Scharrer, E.: The Blood Vessels of Nervous Tissue, Quart. Rev. Biol. **19**:308 (Dec.) 1944.

107. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938.

108. Hoff, E. C.; Grenell, R. G., and Fulton, J. F.: Histopathology of the Central Nervous System After Exposure to High Altitudes, Hypoglycemia and Other Conditions Associated with Central Anoxia, Medicine **24**:161 (May) 1945.

phosphocreatine and phospholipids. Although composing much of nerve tissue, the brain lipids—cholesterol, cephalin, lecithin and sphingomyelin—do not enter into energy-producing metabolism, but rather function only as insulation of neighboring neurons from one another.[109]

Morphologic changes of the brain in congenital cyanosis appear similar to those produced by anoxia from whatever cause—rarefied air, carbon monoxide poisoning, suffocation, anemia and anesthesia. It may be true, however, that the changes in uncomplicated anoxic anoxia are less severe and not so extensive.[110] The "common mechanism" of pathologic change is a complex one involving structural, functional and metabolic factors, and much evidence supports the idea of gradience in the various reactions. Chemical factors accompanying anoxia and possibly playing ancillary roles in neuronal damage are hypoglycemia, hypercapnia and increased extracellular potassium.[111]

One of the functions of oxygen may be to control polarization of cell membranes. Anoxia produced by inhalation of pure nitrogen causes increased frequency of the predominant waves of the electroencephalogram and a gradual increase in wave amplitude. Breathing of room air brings about gradual reversal of electroencephalographic tracings to normal.[112]

Hypoxemia at high altitudes in mountains, such as the Andes, causes restless, unrefreshing sleep disturbed by dreams of an unusually imaginative and apprehensive character.[113] Before acclimatization, newcomers to the region have illusory and fantastic dreams, the most vivid of which are experienced by persons with greatest physiologic disabilities —a point which psychoanalysts may find incongruous with their concept of the significance of dreams.[114]

Death of tissues is not synchronous or simultaneous. The brain seems to be the first to die and the last to respond to revival. Clinical death in many instances represents a reversible transition from life to death. Carotid blood pressure readings and eyeground examinations indicate that there is no blood circulation through the brain during clinical death. Inasmuch as vital portions of the central nervous

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109. Best and Taylor, [59b] pp. 793-796.

110. Lewey, F. H.: Histologic Changes in the Brain Resulting from Various Anoxic Conditions, Arch. Neurol. & Psychiat. **55**:425 (April) 1946.

111. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558 (Nov.) 1938.

112. Gibbs, F. A., and Davis, H.: Changes in the Human Electrocardiogram Associated with Loss of Consciousness, Am. J. Physiol. **113**:49 (Sept.) 1935.

113. MacFarland, R. A.: Psycho-Physiological Studies at High Altitudes in the Andes, J. Comp. Psychol. **24**:147 (Aug.) 1937.

114. Van Liere, E. J.: Anoxia: Its Effects on the Body, Chicago, University of Chicago Press, 1942, pp. 226-237.

system cannot withstand oxygen deficiency longer than five to six minutes, it must be assumed that complete and lasting recovery from clinical death will follow only if revival is accomplished during these first few minutes.[115]

In recent reports of convulsive disorders in children, approximately 14 per cent seemed to stem from cerebral injury due to anesthesia or sedation of the mother and apnea of the child during the natal period.[116] Obstetricians, and perhaps pediatricians, are thinking too much in terms of comfort and rapid delivery of the mother, intracranial injuries and hemorrhages of the infant at birth and too little in terms of neonatal apnea and cerebral anoxia. This condition will leave the brain permanently damaged, while permitting the baby to live.[117] Suffice it here to say the unwise use of analgesics in labor may subject an infant to a series of anoxic insults with cumulative and disastrous effects on the central nervous system.[118]

Figures 1 to 8 are drawings and photographs depicting the salient features of the 3 patients whose cases are presented.

SUMMARY

Since the dawn of civilization, man has been curious about the gaseous interchange between himself and his environment. This curiosity has led to discovery of the gases involved, of much about the mechanics of transportation to and from tissues and of something about the control of breathing and the nature of cellular respiration. From the medical thesaurus are chosen a few of the numerous valuable contributions to present knowledge of respiratory physiology and asphyxia. Accumulated evidence leads to the belief that the central

115. Negovski, V. A.: Agonal States and Clinical Death: Problems in Revival of Organisms, Am. Rev. Soviet Med. **3**:339 (April) 1946.

116. Peterman, M. G.: Convulsions in Childhood: Twenty Year Study of Twenty-Five Hundred Cases, Am. J. Dis. Child. **72**:399 (Oct.) 1946.

117. Burt, E. F.: Pathologic Lesions of Asphyxia Neonatorum, Pennsylvania M. J. **46**:1053 (July) 1943. Schrieber, F.: Apnea of the Newborn and Associated Cerebral Injury, J. A. M. A. **111**:1263 (Oct. 1) 1938; Neurologic Sequelae of Paranatal Asphyxia, J. Pediat. **16**:297 (March) 1940. Darke, R. A.: Late Effects of Severe Aspyhxia Neonatorum, ibid. **24**:148 (Feb.) 1944. Lamm, S. S.: Asphyxia as a Cause of Mental Deficiency: Suggestions as to Prevention, Am. J. Ment. Deficiency **48**:131 (Oct.) 1943. Windle, W. F.: Structural and Functional Alterations in the Brain Following Neonatal Asphyxia, Psychosom. Med. **6**:155 (April) 1944. Clifford, S. H.: The Effects of Asphyxia on the Newborn Infant, J. Pediat. **18**:567 (May) 1941.

118. Faber, H. K.: Cerebral Damage in Infants and in Children: Some Observations on Its Causes and the Possibilities of Its Prevention, Am. J. Dis. Child. **74**:1 (July) 1947.

nervous system bears the brunt of any disturbance in gaseous exchange, regardless of its type or cause.

Three cases of uncomplicated cerebral hypoxia accompanying congenital heart disease are presented. Together, these 3 cases showed neuronal degeneration and necrosis in various degrees of severity and extent, glial reactions ranging from disappearance to hyperplasia and vascular changes varying from dilatation to proliferation. Gross hemorrhages, softenings and cysts, often described in cases of death due to carbon monoxide and anesthetic agents, were not observed.

Particular attention is drawn to the natal period and to the importance of maternal anesthesia and infantile apnea as factors which, if not judiciously controlled, may rapidly produce irreversible changes in the child's central nervous system, with consequent neurologic symptoms and impairment of mentality.

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KLEBSIELLA PNEUMONIAE ASSOCIATED WITH INFANTILE DIARRHEA

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THE CLINICAL features of an epidemic of diarrhea involving infants from 6 weeks to 10 months of age were reported in January 1946.[1] The organism recovered from the stools of the sick infants was classified as "Bacillus mucosus capsulatus" (Klebsiella pneumoniae). With the use of the biochemical tests as a means of identification, the organism would have been classified as Aerobacter aerogenes. However, in a comparative study of organisms of the Friedländer and coli-aerogenes groups it had been observed [2] that known Friedländer organisms gave biochemical reactions characteristic of the coli-aerogenes group and that some strains which had been identified with the usual biochemical criteria as A. aerogenes were observed to possess antigens in common with the three Friedländer types, A, B and C.

Therefore, it was thought advisable to employ serologic methods in an effort to classify the organisms more adequately.

PROCEDURE AND RESULTS

Four strains of organisms, one each of the Friedländer A and Friedländer B types recovered from adults with pneumonia and identified by quellung reaction and two representative strains of B. mucosus capsulatus recovered during the epidemic of diarrhea and arbitrarily called K and M, were selected for the serologic work. Both formalized and heat-killed organisms of strains K and M were used in the study.

After adequate growth in beef heart infusion broth was obtained, the cultures were centrifuged, washed and suspended in saline solution. Strains K and M of B. mucosus capsulatus, those hereafter further identified by the subscript *f*, were

This study was aided by a grant from the Fluid Research Fund of the Yale University School of Medicine.

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1. Walcher, D. N.: "Bacillus Mucosus Capsulatus" in Infantile Diarrhea, J. Clin. Investigation **25**:103, 1946.

2. Osterman, E., and Rettger, L. F.: A Comparative Study of Organisms of the Friedländer and Coli-Aerogenes Groups, J. Bact. **42**:699, 1941. Osterman, E.: A Systematic Study of Encapsulated Gram-Negative Organisms with Special References to Relationships Between Friedländer and Coli-Aerogenes Groups, Dissert., Yale University, 1940.

formalized, while those with the subscript *h* were heat killed at 60 C. The saline suspensions of the Friedländer organisms types A and B were heat killed. It required from one to four hours at 60 C. to check all growth.

Five rabbits were test bled to determine the possible presence of normally occurring agglutinins for B. mucosus capsulatus. Rabbits were given injections daily the first three days of each week, using 0.5 cc. the first week, 1 cc. the second week, 1.5 cc. the third week and 2 cc. the fourth week. Test bleedings were done five days after the last injection. When a sufficiently high titer had not been produced, the rabbits were subjected to a second series of injections, using

TABLE 1.—*Agglutination Reactions Between Test Serums and Strains of Escherichia Coli*

Antigen E. Coli, Strain No.	Antiserum (Rabbit) for Friedländer Types				Strains of B. Mucosus Capsulatus							
	A		B		Kf		Kh		Mf		Mh	
	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	1+	0	0	0	±	0	±	±	0	0
3	2+	1+	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 2.—*Agglutination Reactions Between Test Serums and Strains of Aerobacter Aerogenes*

Antigen A. Aerogenes, Strain No.	Antiserum (Rabbit) for Friedländer Types				Strains of B. Mucosus Capsulatus							
	A		B		Kf		Kh		Mf		Mh	
	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
075	0	0	0	0	0	0	0	0	0	0	0	0
379	2+	2+	2+	3+	2+	2+	2+	2+	2+	2+	2+	2+
382	0	0	0	0	0	0	0	0	0	0	0	0
442	0	0	0	0	0	0	0	0	0	0	0	0
446	0	0	0	0	0	0	0	0	0	0	0	0
561	0	0	0	0	0	0	0	0	0	0	0	0
838	0	0	0	0	0	0	0	0	0	0	0	0
849	0	0	0	0	0	0	0	0	0	0	0	0
252	0	0	0	0	0	0	0	0	0	0	0	0
246	0	0	0	0	0	0	0	0	0	0	0	0

the same schedule, but only 2 cc. amounts. It was necessary to employ a second series of injections in most instances. The rabbit serums thus produced were tested against Friedländer A and B organisms, organisms recovered from persons with the epidemic diarrhea, A. aerogenes and Escherichia coli. The strains of A. aerogenes and the E. coli were selected on the basis of their colonial and morphologic appearance and their biochemical reactions.

Ten strains each of E. coli and A. aerogenes were tested against the rabbit antiserums (table 1 and 2). One strain each of Friedländer A and Friedländer B was tested against the rabbit antiserums (table 3), and six strains of B. mucosus capsulatus recovered from 6 different children during the epidemic of diarrhea were also tested against the rabbit antiserums (table 4).

From the data in tables 1 and 2, it is apparent that the antiserums reacted poorly with 2 of the 10 strains of E. coli and only moderately well with 1 of the strains of A. aerogenes. However, in tables 3 and 4, it may be seen that, with few exceptions, there was definite agglutination with Friedländer A and B organisms and with B. mucosus capsulatus.

This suggested that strains of B. mucosus capsulatus possessed antigens in common with the Friedländer A and Friedländer B types. It was also apparent that strains of E. coli and A. aerogenes did not possess antigens in common in significant titer with either B. mucosus capsulatus or the Friedländer A or B types.

The rabbit serum was then adsorbed with E. coli and with A. aerogenes. Adsorption studies were done with incubation of the organisms with the antiserum for thirty minutes, one hour and four hours. No change in the ability of the serum to agglutinate B. mucosus capsulatus was detected.

TABLE 3.—*Agglutination Reactions Between Test Serums and Strains of Friedländer Organisms*

Antigen Friedländer Strains	Antiserum (Rabbit) for Friedländer Types				Strains of B. Mucosus Capsulatus							
	A		B		Kr		Kh		Mr		Mh	
	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
Type A	4+	4+	0	0	3+	3+	4+	4+	3+	3+	3+	3+
Type B	4+	4+	4+	4+	2+	2+	4+	4+	4+	4+	4+	4+

TABLE 4.—*Agglutination Reactions Between Test Serums and Strains from Patients with Epidemic Diarrhea*

Antigen B. Mucosus Capsulatus Strain No.	Antiserum (Rabbit) for Friedländer Types				Strains of B. Mucosus Capsulatus							
	A		B		Kr		Kh		Mr		Mh	
	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
K	4+	4+	3+	2+	3+	3+	4+	4+	4+	4+	3+	2+
L	3+	1+	0	1+	1+	1+	2+	0	0	0	0	0
M	4+	4+	4+	4+	4+	4+	2+	4+	4+	4+	4+	4+
N	±	0	2+	2+	4+	4+	1+	0	3+	3+	±	+
O	1+	0	±	±	0	0	1+	0	0	0	1+	1+
P	1+	1+	2+	2+	3+	2+	3+	2+	1+	1+	4+	4+

When the rabbit serum was adsorbed with Friedländer A, Friedländer B or B. mucosus capsulatus, all the agglutinating antibodies for Friedländer A, Friedländer B or B. mucosus capsulatus were completely removed. This cross reaction in adsorption could not be made selective with respect to Friedländer types by varying the amount of the inoculum or the duration of incubation of the antiserum with the organisms.

Friedländer C organisms were not employed in this study as quellung serum for identification of this strain is not commercially prepared.

It was felt that there was no significant variation in the results obtained with either formalized or heat-killed organisms in the preparation of the antiserum.

The consistently strong agglutination reactions given by strain 379 of A. aerogenes to all the antiserums suggest that this organism is a member of the Friedländer group rather than of the Aerobacter group.

SUMMARY

A common antigen was demonstrated in types A and B of the Friedländer bacillus and in a group of bacterial strains isolated from patients with infantile diarrhea. Adsorption of an immune serum for any one strain with one organism removed the agglutinating antibodies for all strains.

A common antigen could not be demonstrated among Aerobacter aerogenes, Escherichia coli and the organisms isolated from patients with infantile diarrhea in either agglutination or adsorption tests.

Indiana University Medical Center (7).

HISTOPLASMIN PATCH TEST

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NEW YORK

AN ATTEMPT was made to develop a histoplasmin patch test similar to the tuberculin patch test. Since many analogies exist between histoplasmosis and tuberculosis, such a test was expected to be practicable.

Histoplasmin patch tests were prepared in the following way: 16 square centimeters of thin filter paper was saturated with a solution consisting of 0.5 cc. of undiluted histoplasmin (obtained from Hixon Memorial Laboratory, University of Kansas Hospital, United States Public Health Service, Kansas City, Kan.) and 0.2 cc. of pure glycerin. After drying, the filter paper was cut into small squares, each 25 square millimeters in size.

The patch tests were applied for forty-eight hours to the skin of 64 children who were positive reactors to the intracutaneous histoplasmin test.[1] The skin reactions were read after removal of the patches and forty-eight hours later. None of the children showed a positive reaction to the histoplasmin patch test.

A further trial with a higher concentration of antigen was made. for this purpose, a piece of filter paper was saturated with the same undiluted histoplasmin and dried, six times in succession. The patch tests prepared with this filter paper contained about six times the histoplasmin concentration of the first batch. Eleven positive reactors to the intracutaneous histoplasmin test were tested with this stronger histoplasmin patch. No positive skin reactions were obtained.

It is doubtful whether this failure can be reversed by the use of still higher histoplasmin concentrations. This doubt is based on previous experiences[2] with tuberculin patch tests made up with highly diluted tuberculin. Among 106 positive reactors to the Mantoux test using 0.01 mg. of old tuberculin, 21 children showed positive reactions even to patch tests made from a 1:100 dilution of standard strength tuberculin, and as many as 62 children to 1:20 strength tuberculin patch tests.

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1. The histoplasmin patch tests were used in the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tenn. Dr. Amos Christie cooperated in this study.

2. Vollmer, H.; Zelson, C., and Rubin, H.: J. Pediat. **15**:508, 1939.

No satisfactory explanation can be offered for the failure of the histoplasmin patch test. Similar failures of the patch test principle were observed in the past with extracts of other fungi, such as trichophyton and saccharomyces, in high concentrations.

SUMMARY

With the method here described, histoplasmin patch tests did not elicit skin reactions in positive reactors to the intracutaneous histoplasmin test.

25 Central Park West (23).

URINARY GLYCOCYAMINE, CREATINE AND CREATININE

II. Their Excretion in Children with the Nephrotic Syndrome

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AND
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THE pathogenesis of the nephrotic syndrome is not entirely clear. The alterations in the electrophoretic pattern of the serum and its albumin fractions in nephrotic patients,[1] along with changes in the esterase activity of their plasma,[2] have focused attention on the liver as the source of these modifications.[3] These reports, however, have not been conclusive.

A study of any metabolic process involving the integrity of both renal and hepatic activity for its ultimate consummation would be helpful in the evaluation of the role played by each organ. This observation would be particularly true, if, knowing the specific function of each organ involved, one could measure alterations in the intermediate and end products of the metabolic cycle in nephrotic subjects. It might then be possible to indicate the system at fault.

The metabolism of creatinine lends itself well to such an investigation. The process is initiated in the renal epithelium where glycocyamine, or guanidoacetic acid, is synthesized from the two amino acids, arginine and glycine.[4] About 5 per cent of this glycocyamine is excreted in the normal adult urine.[5] The remainder is transported to the liver, where it receives a labile methyl group to form creatine, or methyl glycocyamine.[6] Part of this is excreted as free creatine, but

From the Children's Department, St. Mary's Hospital.

1. Stern, K. G., and Reiner, M.: Electrophoresis in Medicine, Yale J. Biol. & Med. **19**:67-99 (Oct.) 1946.

2. Kunkel, H. G., and Ward, S. M.: Plasma Esterase Activity in Patients with Liver Disease and the Nephrotic Syndrome, J. Exper. Med. **86**:325-337 (Oct.) 1947.

3. Gottfried, S. P.; Steinman, J. F., and Kramer, B.: Chemical Studies in Children with the Nephrotic Syndrome, Am. J. Dis. Child. **74**:283-304 (Sept.) 1947.

4. Borsook, H., and Dubnoff, J. W.: Formation of Glycocyamine in Animal Tissues, J. Biol. Chem. **138**:389-403 (March) 1941.

5. Borsook, H.; Dubnoff, J. W.; Lilly, J. C., and Marriott, W.: Formation of Glycocyamine in Man and Its Urinary Excretion, J. Biol. Chem. **138**:405-410 (March) 1941.

6. Borsook, H., and Dubnoff, J.: Methylation of Guanidoacetic Acid by Homocystine Plus Choline with Rat Liver Slices, J. Biol. Chem. **160**:635-636 (Oct.) 1945.

the major portion is converted to its anhydride, creatinine, by the muscles and is excreted as such.

This process can be judged on a quantitative basis. Hoberman and his associates [7] showed that the total creatinine lost daily is replaced by an equimolar amount of creatine, synthesized from equimolar amounts of glycocyamine and methyl groups derived from the methyl donors in the liver. Small defects in the hepatic transmethylation process are reflected by a pronounced increase in the urinary excretion of glycocyamine.

The normal values for infants and children for the urinary excretion of glycocyamine, creatine and creatinine were set up in our preceding report.[8] We used these figures as a basis for comparison with the data obtained from our nephrotic group. Little is known regarding the excretion of glycocyamine in nephritis. Borsook and Dubnoff [4] showed that in a group of persons with chronic nephritis the urinary glycocyamine was reduced.

TABLE 1.—*Data Obtained in Study of Urinary Excretion of Glycocyamine, Creatine and Creatinine in Children and an Adult with Renal Disorders*

Patient	K. K.	D. B.	Y. N.	R. W.	D. D.	S. B.	T. B.	B.
Age, yr.	1½	2	2½	4½	4½	4	4	50
Weight, Kg.	14.3	14.4	12.2	18.9	14.4	16.8	22.1	55.8
24 hr. urinary output, cc.	170	430	290	775	725	314	270	608
Glycocyamine, mg./100 cc. urine	29.2	47.5	29.3	27.4	74.2	55.0	56.3	66.0
Total in 24 hr.	49.6	204.2	84.0	213.3	537.9	172.7	152.0	400.8
Mg./Kg. body weight	3.5	14.1	6.9	11.3	37.3	10.2	6.8	7.1
Creatinine								
Preformed, mg./100 cc. urine	55.0	51.9	43.5	45.6	38.0	117.6	40.7	154.3
Preformed, mg. in 24 hr.	93.5	223.2	126.1	353.3	275.5	349.5	109.9	938.1
Total creatinine, mg./100 cc. urine	117.1	82.9	50.9	55.1	48.2	129.0	74.0	191.7
Total creatinine, mg./24 hr.	199.1	356.5	147.6	427.0	349.4	405.0	199.5	1,165.5
Creatinine coefficient $\left(\frac{\text{Mg. total creatinine in 24 hr.}}{\text{Kg. of body weight}}\right)$	13.9	24.8	12.0	22.6	24.1	24.2	9.0	20.8
Creatine, mg. excreted in 24 hr.	102.5	166.6	24.9	92.1	92.4	69.6	112.0	284.2
Creatine coefficient, mg. creatine/Kg. of body weight	7.1	11.8	2.0	4.8	6.4	4.1	5.02	5.0
Glycocyamine-creatinine coefficient $\left(\frac{\text{Mg. glycocyamine/24 hr.} \times 100}{\text{Mg. total creatinine/24 hr.}}\right)$	24.9	54.5	51.9	50.0	153.6	42.5	76.2	34.3

PROCEDURE

We selected for our study a group of 7 children with the nephrotic syndrome whose ages ranged from 1½ to 4 years. There was also 1 adult woman whose

7. Hoberman, H. D.; Lloyd, C. W., and Williams, R. H.: The Role of the Liver in Guanidoacetic Acid Metabolism in Man, Science **104**:619-621 (Dec. 27) 1946.

8. Flood, R. G., and Pinelli, R. W.: Urinary Glycocyamine, Creatine and Creatinine: I. Their Excretion in Infants and Children, Am. J. Dis. Child. **77**:740 (June) 1949.

condition was diagnosed as prerenal proteinuria. The term "nephrotic syndrome" was used to denote a condition in which albuminuria, hyperproteinuria and edema were the outstanding clinical findings without evidence of progressive renal insufficiency. Prerenal proteinuria may be defined as the condition in which serious albuminuria exists without demonstrable renal pathologic change. All these determinations were made on the children at their initial admission to the hospital, before any therapy had been instituted.

The procedure for the collection of the samples of urine and the methods used in the determinations were the same as those described in our preceding report.[8] The only difference was the precipitation of the protein from the urine by chloroform prior to the determinations, as described by Hoberman.[9]

The rate of secretion of the various components was expressed, as in our previous paper, as the coefficient of the specific substance, namely, in milligrams per kilogram of body weight excreted in twenty-four hours. The relationship between the urinary glycocyamine and the total creatinine was expressed as a

TABLE 2.—*Summary of the Ranges and Means in Values Obtained in Normal Children and in Those with Nephrosis*

	Normal Children	Nephrotic Children
Number of observations	7	7
Age range, years	1½ to 4	1 to 7
Glycocyamine coefficient		
Mean	1.34	12.87
Range	0.9 to 1.7	6.8 to 37.3
Creatinine coefficient		
Mean	24.85	18.65
Range	16.3 to 36.2	9.0 to 24.8
Creatine coefficient		
Mean	5.81	5.88
Range	0.8 to 9.2	2.0 to 11.8
Glycocyamine-creatinine coefficient		
Mean	5.37	64.8
Range	4.3 to 7.6	24.9 to 153.6

coefficient obtained by multiplying the milligrams of glycocyamine excreted in twenty-four hours by 100, then dividing the product by the number of milligrams of total creatinine excreted over the same period. All the observations on the experiment are presented in table 1.

A summary of the ranges and means of the values, along with comparisons with the normal values as established in our preceding paper,[8] are shown in table 2.

OBSERVATIONS

The most striking observation was the tremendous increase in the twenty-four hour urinary output of glycocyamine for the nephrotic group and for the lone patient with prerenal proteinuria. The magnitude of the increment of the mean values for the coefficient of glycocyamine in the nephrotic children amounted to more than 900 per cent of the coefficient observed in the normal children.

9. Hoberman, H. D.: The Determination of Guanidoacetic Acid and Arginine in Human Urine and Serum, J. Biol. Chem. **167**:721-727 (March) 1947.

It was also apparent that the nephrotic child has the ability to concentrate the urinary glycocyamine when the twenty-four hour output of urine is greatly reduced. Several of these children showed a concentration as high as 74 mg. of glycocyamine per hundred cubic centimeters of urine. This phenomenon was observed to a lesser extent in our control group. Here the daily output of glycocyamine was fairly constant per kilogram of body weight and relatively independent of the total volume of urine voided. Furthermore, the severer the nephrosis, as judged by clinical tests, the greater was the amount of glycocyamine appearing in the urine.

The difference in the rate of secretion of total creatinine between the two groups was not so remarkable. However, there was a definite trend for the nephrotic children to secrete less total creatinine in twenty-four hours than the normal group.

The significance of this observation becomes questionable when one considers that the body weights of the nephrotic children represented an undetermined amount of body water because of the existing edema. The effect of this amount of body water would be to lower the total creatinine coefficient, as it expresses the amount of creatinine excreted per kilogram of body weight, and the important factor in this weight, as far as we are concerned, is active muscle weight.

We might have made a correction for the edema by computing the body surface of each child and using this as a standard of comparison. However, in this preliminary report we wished to present the facts as found.

The rate of secretion of creatine did not vary greatly in the two groups. The glycocyamine-creatinine coefficient, which is a measure of the relationship of glycocyamine to total creatinine voided in twenty-four hours, was decidedly increased in the nephrotic group, as would be expected with an increased rate of excretion of glycocyamine and a decreasing output of total creatinine.

COMMENT

From these observations we may conclude that in both the nephrotic group and in our single patient with prerenal proteinuria there was an increased rate of secretion of glycocyamine and a questionable decrease in the urinary output of total creatinine as well.

If we could substantiate the statement that the output of urinary creatinine was below that of the normal child, we might assume, in accordance with the premise of Hoberman and associates,[7] that the fault lay in the transmethylation process of liver. We might then assume that an excessive amount of glycocyamine is lost in the urine because it is not being bound in the liver as creatine by proper methylation.

When the creatinine coefficients of the nephrotic children were examined individually, we found several extremely low values. These occurred usually in the child with the severest clinical nephrosis and in the child with the next to the highest output of glycocyamine. These low values were offset by the results of three determinations which approached normal.

If the increased output of glycocyamine in the nephrotic group is due either to increased renal permeability or to impaired reabsorption by the tubules, we must change our conception of the state of prerenal proteinuria, as this condition shows the same phenomenon. If the fault does not lie in the renal mechanism, then the increased output of glycocyamine must be due to deficient transmethylation in the hepatic cells. While we cannot prove from our figures that the transmethylation process of the liver is at fault, we feel that there is enough suggestive evidence to indicate such a trend.

The function of the striated muscles producing the anhydride, creatinine, from creatine is apparently intact in the nephrotic child.

SUMMARY

A group of 7 nephrotic children and 1 adult with prerenal proteinuria were studied as to their daily urinary output of glycocyamine, creatine and creatinine. The data so obtained are compared with those from a similar group of normal controls.

The nephrotic group demonstrated a tremendous increase in the output of urinary glycocyamine above the normal. This increase was also observed in the woman with prerenal proteinuria.

There was a trend for the amount of total creatinine excreted over a period of twenty-four hours to be reduced. However, this tendency could not be fully substantiated as it was computed on a basis of milligrams per kilogram of body weight and these children were all edematous.

The possibility of a defective transmethylation process of the liver as a cause for the excessive secretion of urinary glycocyamine is discussed.

The creatine excretion in the nephrotic persons was within normal limits.

490 Post Street.

TOXIC LEVEL OF FLUORINE IN WATER SUPPLIES

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HOBBS, N. MEX.

I BELIEVE the experiment of putting 1 part per million of flourine in the municipal water supplies of various cities which is now in progress in order to prevent tooth decay, is being prematurely tried. Fluorine as related to tooth decay has not had nearly the exhaustive study dental fluorosis has had. There is no quarrel as to the validity of both conditions, but there has not been established by all investigators the amount of fluorine which is nontoxic and also effective in prevention of tooth decay.

The United States Public Health Service, which is fostering this experiment, stated that 1 part per million (p. p. m.) is not toxic, basing this observation, for the most part, on the work of Dean.[1] In their investigation on the relation between fluorine and dental caries a simultaneous study was not made regarding dental fluorosis.[2]

There are several areas in the United States where the water has a natural fluorine content of 1 p.p.m. I am practicing in such an area. In 1937, after moving from Michigan to eastern New Mexico, I was impressed by the number of attractive young persons who were disfigured by defective teeth, which defects on cursory notice looked like severe decay. I had never before seen dental fluorosis. I asked several of the patients what was wrong with their teeth and the reply was invariably, "Texas teeth!"

I then began reviewing the literature and examining the school children in this city and published an article on the subject in 1938.[3] A mild to moderate defect in the enamel of the secondary teeth was present in about 18 per cent of the children. Therefore, in an attempt to produce flawless secondary incisors, ingestion of distilled water was recommended for all children under 6 years of age, and certainly for those under 3.

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1. Dean, H. T.: Fluorine and Dental Caries, Am. J. Orthodontics (Oral Surg. Sect.) **33**:49-67 (Feb.) 1947.

2. Dean, H. T.: Dental Caries and Fluorine, American Association for the Advancement of Science, 1947, pp. 5-31.

3. Badger, D. C.: Dental Fluorosis in Lea County, New Mexico, Southwestern Med. **22**:317-318 (Aug.) 1938.

RESULTS OF OTHER INVESTIGATORS

There has been no absolute and definite agreement among investigators as to the minimum toxic dose of fluorine in respect to dental fluorosis. The workers who have done the most comprehensive animal experimentation, Smith and his associates, of the University of Arizona, set the top limit as 0.9 p.p.m.[4]

In 1944, when the United States Public Health Service was instituting the present experiment of adding fluorine in the concentration of 1 p.p.m., I wrote both to *The Journal of the American Medical Association* and to Dr. Smith; to the American Medical Association questioning the advisability of the experiment, and to Dr. Smith for a résumé of the findings of his associates and him.

Dr. Smith wrote in detail and corroborated their previous observations and added that, whereas he and his associates before had stated that 0.9 p.p.m. of fluorine was toxic, they now dropped the level to 0.8 p.p.m.[5] The opinion was expressed that, with the increased use of fluorine sprays for fruit trees, the possibility for ingestion of fluorine is greatly increased.[6]

As a result of the testimony of Dr. Smith and his co-workers[5] for the United States Food and Drug Administration, it was established that the fluorine in a safe fruit spray would not exceed 7 p.p.m. They pointed out the amount of fluorine that would be ingested by the following simple calculation: Assume that an apple containing 7 p.p.m. is consumed daily during the apple season. Assume the weight of an apple to be 1.16 Kg., or 166 Gm. Each apple then contains 1.16 mg. of fluorine or the equivalent of 1.16 p.p.m. of fluorine in a liter of water. This would cause a mild mottling of the enamel if apples are eaten consistently, even though there is no fluorine in the drinking water.[5]

RESULTS OF PRESENT SURVEYS

I made two surveys in this city, where fluorine naturally occurs in drinking water in a concentration of 1 p.p.m. Both were consistent in that there was roughly one third of those surveyed who had some defect of enamel. However, because of current statements concerning the toxic level, the second survey was broken down and statistics gathered more carefully.

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4. Smith, H. V., and others: Mottled Enamel in the Salt River Valley and Fluorine Content of the Water Supplies, Technical Bulletin 61, Tucson, Arizona, University of Arizona, May 15, 1936.

5. Smith, H. V.: Personal communication to the author.

6. Smith, M.: Fluorine Toxicosis: Public Health Problem, Am. J. Pub. Health **25**:696-702 (June) 1935.

School children who had their permanent central incisors were examined, as it was felt that these would be the important teeth from a practical point of view. Only those children who had been born and reared in this city were included. Each child's history was checked as to whether he had lived away from home for any period exceeding two months, and those who had were eliminated. This is important, since there are many areas within 20 miles (32 km.) in which water has a natural content of 2.5 p.p.m.

This town also has a migratory population because of the fact that it is in an oil-producing country and the workers move from town to town depending on drilling activity in any particular section. Ninety children were left after this screening. Approximately 300 children were examined initially. Of this group of 90 children, 28 had some defect of enamel. Because this number was larger than I had expected, I divided the children into three subgroups.

Photograph showing typical defect of dental fluorosis.

The first subgroup was composed of those who had received distilled water as their drinking water in the first two years of life. There were 9 children in this group and none of them had a defect.

The second subgroup contained those children who had received water from the municipal water supply. In this group there were 65 children. Eighteen, or 36 per cent, had some defect of enamel. A sample of water was taken and sent to the University of New Mexico, Albuquerque, N. Mex., for fluorine analysis and the content was reported as 0.9 p.p.m. The defect which I have noted is not severe, but the tooth is definitely far from flawless. The mild defect is a white streaking of the enamel with some pitting, varying in size from pinhead to pinpoint. None of the teeth had any discoloration of the pitting. A picture of such teeth was attempted with an ordinary camera and daylight exposure which, though poor, shows some of the qualities of this defect.

I am unable to explain this high percentage, as from past statistical surveys only when the water has 1.3 to 1.6 p.p.m. should one expect this percentage of mild mottling. I have talked with water drillers here (all water supplies are from artesian wells), and they expressed the

opinion that all the water sands are connected. There is a higher concentration of fluorine in outlying wells, which I shall cite later. However, all the water analyses of the municipal supply have shown from 1 to 0.9 p.p.m.

The use of fluorine sprays on fruit during the past ten years may have increased the percentage. The volume of water drunk is also a factor. If the consumption of water is twice the usual amount, there would be an increase in the incidence of dental fluorosis. The climate in this area is hot and dry, and it is logical to assume that some of the increase in incidence is due to more water drunk.

The third subgroup consisted of 16 children who had used water from private wells. Six of the children had normal teeth. Ten of the children had a defect. The well water was analyzed, and because of the variation these analyses are cited individually.

Patient	Dental Fluorosis	Well Depth, Ft.	Fluorine, P.P.M.
B. B.	2+	92	...
B. D.	1+	60	...
L. F.	2+	80	...
P. G.	1+	90	...
D. C.	Negative	65	...
D. G.	2+	90	1.4 (see figure)
M. G.	2+	60	1.2
S. H.	2+	40	0.9
B. L.	1+	60	1.0
J. R.	Negative	55	...
R. R.	Negative	80	1.1
W. S.	2+	60	...
J. S.	Negative	98	...
J. W.	Negative	60	...

COMMENT

With so few cases, it is impossible absolutely to determine the toxic level, but, among the children examined, dental fluorosis was observed in 30 per cent of the children who drank water containing 0.9 p.p.m. of fluorine.

From the reports on hand and because there is some controversy regarding the toxic level of fluorine, I believe that the widespread use of fluorinated water is a faulty procedure and will lead to unhappy results.

SUMMARY AND CONCLUSIONS

1. If fluorine is added to the municipal water supplies, the level should be lowered to 0.7 p.p.m.

2. If the level of fluorine is above 0.7 p.p.m., then children under 3 years of age, and preferably under 6, should use filtered or distilled water in order to prevent a defect in their permanent teeth, which are forming during these years.

3. The damage from the ingestion of fluorine comes during the calcification of the secondary teeth, which occurs during the first six years of life (with the exception of the second and third molars), and during this period tooth decay is not important. Therefore, there should be a chronologic division of the population as to when fluorine is used.

4. From my study, dental fluorosis does occur at a fluorine level of 0.9 p.p.m., and extraneous factors are probably no different here than in other sections of the country.

200 North Dalmont.

Case Reports

CYANOSIS CAUSED BY METHEMOGLOBINEMIA

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CYANOSIS in infancy due to methemoglobinemia following ingestion of well water containing nitrates does not seem to be a rare condition, yet a review of the literature reveals relatively few cases recorded.

Methemoglobinemia may follow administration of such chemicals as aniline, nitrophenol, sulfanilamide, potassium chlorate and nitrates.

A recent review of the subject by Comly [1] offered an explanation of the reason infants may be more susceptible to methemoglobinemia than adults. In the case to be reported there may be a dual causative basis or a synergistic action of two factors: nitrates in well water and acetophenetidin U. S. P. (phenacetin®).

Comly [1] stated that, although no definite statement can be made, it seems advisable to recommend that well water used in infant feeding possess a nitrate content no higher than 10, or at the most 20, parts per million.

REPORT OF A CASE

A 22 day old infant was admitted to St. Joseph Infirmary, Aug. 18, 1947, with the chief complaint, as given by the father, "baby is black." The day prior to his admission, it was suspected by the family that the infant had fever. The child had coughed a few times, and the family physician was consulted. He telephoned a prescription of acetophenetidin, 0.085 grain (0.0051 Gm.), acetylsalicylic acid, 0.166 grain (0.01 Gm.), with syrup of cherry N. F. and compound elixir of pepsin N. F., to be given every three hours.

The first dose of this medicine was administered at 7 p. m., August 17. Soon afterward, without evidence of choking, the baby became blue. As the infant and parents are dark complexioned, nothing was thought to be abnormal. Two more doses of the prescription were given, and by morning the child was almost black. The physician was again summoned, and he advised hospitalization.

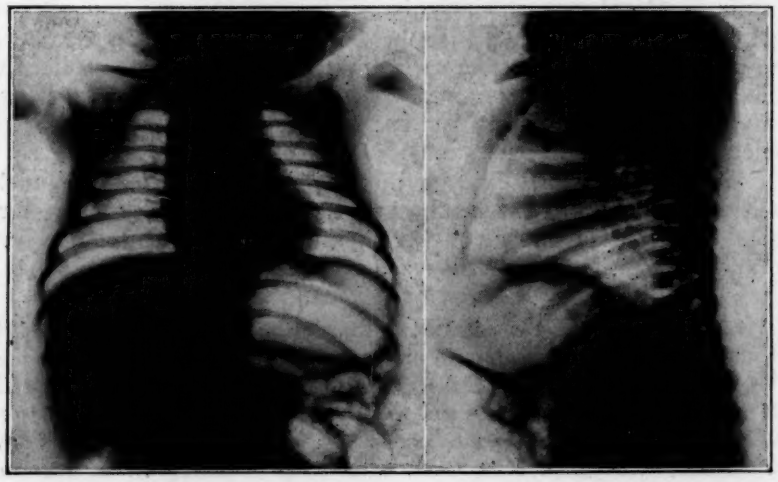
The past history revealed a normal spontaneous delivery without difficulty. The infant was cyanotic at birth, and oxygen was administered for forty-eight hours. A review of the record failed to reveal the cause of the cyanosis. Results of the physical examination at this time were entirely normal. The feedings consisted of evaporated milk, water and dextri-maltose.® There had been no vomiting or diarrhea. The family history was not remarkable, except that the mother had a postpartum hemorrhage which required hospitalization three weeks after the child's birth.

From the Department of Pediatrics, University of Louisville School of Medicine, services of James W. Bruce, M.D., and W. W. Nicholson, M.D.

1. Comly, H. H.: Cyanosis in Infants Caused by Nitrates in Well Water, J. A. M. A. **129**:112 (Sept. 8) 1945.

Physical examination on the infant's admission to the hospital revealed a rectal temperature of 100.2 F.; the pulse rate was 110 and respirations 25 per minute. The infant's weight was 8 pounds (3,629 Gm.). The skin was extremely cyanotic, yet it felt warm and elastic. The remaining results of the entire examination were absolutely normal. The roentgenogram of the chest (see figure) was normal in appearance. Except for a slight trace of albumin, the urinalysis showed no abnormality. The blood study revealed a red cell count of 4,530,000 per cubic millimeter and a hemoglobin concentration of 84 per cent. There were 16,000 white blood cells per cubic millimeter, with a differential count of 53 per cent neutrophils, 48 per cent lymphocytes and 5 per cent monocytes.

The infant was immediately placed in an oxygen tent, but after several hours there was no improvement in the color. Administration of nikethamide (coramine®), 2 minims (0.12 cc.) subcutaneously, made no significant change in the cyanosis. The rectal temperature fluctuated from 100.8 to 102.0 F.



Roentgenograms of the chest of infant with cyanosis caused by methemoglobinemia. Note normal appearance of thoracic region.

In view of the lack of positive findings, but a rise in temperature, sodium penicillin, 30,000 units, was given intramuscularly every three hours. Further efforts were made to disclose some extrinsic factor producing the cyanosis, such as shoe dye, a cooking gas, refrigerant gas or disinfectant, but nothing positive could be elicited. Since cyanosis in infancy [2] due to methemoglobinemia had been observed, it was decided to requestion the family regarding the use of well water. Much to my surprise, it was found that, even though the family lived in the city, well water was being used in the preparation of the infant's formula, which consisted of 7 ounces (207 cc.) of evaporated milk, 14 ounces (414 cc.) of water and 2 tablespoons (30 cc.) of dextri-maltose.® With this additional fact, spectroscopic examination of the blood was made August 19, which revealed 1.6 Gm. of methemoglobin per hundred cubic centimeters of blood. Immediately, 5 mg. of methylthionine chloride U. S. P. was administered

2. Scott, E. P.; Prince, G. E., and Rotondo, C. C.: Dye Poisoning in Infancy, J. Pediat. **28**:713 (June) 1946.

intravenously; within one hour the cyanosis had completely cleared, and the infant was removed from the oxygen box. As the temperature was elevated, the penicillin was continued for three days. The cyanosis never returned, and the infant was discharged from the hospital August 22. The parents were instructed to use distilled water in the preparation of the formula.

Analysis of the well water done August 21 revealed increased nitrates, and a complete analysis done by a commercial analytic laboratory revealed 14 parts per million.

The infant was seen October 30, at the age of 3 months; he was gaining weight, and there had been no recurrence of the cyanosis. Results of a complete blood count were within normal limits. On December 19 he weighed 15 pounds 9 ounces (7,059 Gm.), and physical examination showed no abnormality.

COMMENT

Obviously, the cause of the cyanosis in the case was the methemoglobinemia. It is possible that one or more factors may have been acting in the production of the methemoglobinemia, viz., nitrates in the well water, acetylsalicylic acid or acetophenetidin, or the infection of the respiratory tract as manifested by fever, elevated white blood cell count and cough. Any one of these factors, or a synergistic action of more than one, may have produced the methemoglobinemia.

It was suggested to the parents that they try the well water or the original prescription again, but they refused the idea.

The condition apparently occurs commonly in rural areas, but a careful history should be obtained in all cases of unexplained cyanosis, as some urban inhabitants use well water in the preparation of infants' formulas.

Since one cannot say that the drugs used in a case such as this did not act separately or synergistically in the production of the methemoglobinemia, symptomatic therapy should be limited always to the simplest medicaments.

SUMMARY

Cyanosis produced by methemoglobinemia in a 22 day old infant is herein reported. The administration of methylthionine chloride intravenously promptly relieved the cyanosis.

1617 Heyburn Building (2).

CHRONIC RELAPSING PANCREATITIS AND HYPERLIPEMIA

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and
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CHRONIC relapsing pancreatitis is rare in childhood. Only 2 of the 29 cases reported by Comfort, Gambill and Baggenstoss[1] in 1946 were in children. Hyperlipemia was not coexistent with the pancreatitis in either of these cases. Thannhauser,[2] in 1940, included in his classification of the lipidoses hyperlipemia with secondary xanthomatosis associated with chronic pancreatitis, which he reported as occurring in adults. The rarity of this condition in children warrants the following case report. In this case, determinations of the enzymes and lipids in the blood, the fat and nitrogen in the stools, and the duodenal enzymes were made in the Division of Biochemistry, Mayo Clinic.

REPORT OF CASE

A white boy, 8 years of age, was brought to the Mayo Clinic because of attacks of severe abdominal pain which had been recurring from the time he was 4 years old. The family history revealed that one younger sibling probably had xanthomatosis of the skin. During the first two years of life, the patient had had spells of vomiting which occurred two or three times a week. Xanthomatous lesions were said to have been present on the skin from the age of 15 months until about the age of 2 years. The lesions disappeared after the child had been placed on a fat-free diet.

At the age of 4 years, he experienced his first attack of abdominal pain, which lasted three days. A diagnosis of acute appendicitis was made and he was operated on. However, at the time of operation, a ruptured abscess of the pancreas was observed. Generalized peritonitis developed, and the child had a stormy convalescence.

After this, he was apparently well until the age of 5 years, when he had a recurrence of abdominal pain which persisted for three days, after which he was again operated on. It was said that at the time of operation numerous adhesions

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From the Section on Pediatrics of the Mayo Clinic (Dr. Kennedy).

Read at the meeting of the Northwestern Pediatric Society, Bayport, Minn., Sept. 26, 1947.

1. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Study of Twenty-Nine Cases Without Associated Disease of the Biliary or Gastro-Intestinal Tract, Gastroenterology **6**:239-285 (April); 376-408 (May) 1946.

2. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, edited by H. A. Christian, New York, Oxford University Press, 1940.

were present in the peritoneal cavity which were thought to have caused obstruction of the small bowel.

At the age of 6 years, the child again complained of abdominal pain. At that time the pain was localized definitely in the left upper quadrant. There were distention of the abdomen, fever and leukocytosis. At operation an ulcer with a crater was observed in the tail of the pancreas. In the opinion of the surgeon this was the site of a second ruptured abscess. There were many peritoneal adhesions, and fluid which was thought to be pus was seen in the peritoneal cavity. Generalized peritonitis was present. After surgical drainage and sulfonamide therapy, the child made a rapid recovery. However, he continued to complain of abdominal pain for three or four days after operation.

About ten months later, acute abdominal pain, which was precipitated by a blow on the abdomen, developed. At operation, peritoneal adhesions were again encountered and intestinal obstruction was said to have been relieved. The pancreas was examined at the time of operation, and the surgeon was of the opinion that little pancreatic tissue remained. Abdominal pain again lasted for three or four

TABLE 1.—*Values for Indicated Substances in the Blood of a Child with Chronic Relapsing Pancreatitis and Hyperlipemia*

			Mg. per 100 Cc.						
					Cholesterol				
							Esters		Phospholipid (Lecithin)
	Units		Total Fat	Fatty Acid	Total	Free	Amount	Per Cent of Total	
Diet and Date	Amylase	Lipase							
General (4/12/47)..	400	0.7	5,100	4,768	332	64	268	80.7	...
High fat (4/25/47)..	106	0.2	3,924	3,552	372	138	234	62.9	606
Elective (5/ 7/47)..	...	...	2,916	2,584	332	86	246	74.1	308
Low fat (5/13/47)..	...	...	1,804	1,576	228	68	160	70.2	376
General (6/ 7/47)..	800	1.3	4,652	4,280	372	98	274	73.7	463
Normal values									
Low.....	80	0	400	250	150	50	100	40	185
High.....	320	0.3	650	400	250	150	175	70	250

days after operation. After recovery from this operation, the child had had several recurrences of mild abdominal pain, one of which was precipitated by trauma. All these attacks subsided without operation.

When he was 7½ years of age, severe abdominal pain and distention again developed. The patient underwent the fifth major surgical procedure. For the third time, a ruptured abscess of the pancreas and pus in the peritoneal cavity were said to have been found. As before, surgical drainage and sulfonamide therapy were instituted. Except for abdominal pain, which lasted for three or four days after the operation, recovery was uneventful. During this attack, mild transient glycosuria was discovered. One month after this attack, he again experienced mild symptoms referable to the abdomen which responded to conservative treatment.

On his arrival at the clinic, the boy was asymptomatic. Physical examination revealed a well developed, well nourished child. There was pallor of the skin. Numerous abdominal scars were present which exhibited keloid formation of mild degree. The liver and spleen were palpable but not greatly enlarged. The results

of routine laboratory examinations were normal. There were no calcified masses demonstrable roentgenologically in the region of the pancreas. The serum of blood that was withdrawn for a flocculation test was chylous.

Values for the serum amylase [3] and serum lipase [4] were slightly elevated. Values for blood lipids [5] revealed definite hyperlipemia. The value for fatty acids was more than ten times the average normal level. The value for phospholipids was more than two times normal, and the value for cholesterol was approximately 50 per cent greater than normal (table 1). The curve for dextrose tolerance was flat. Maclagan's [6] thymol turbidity test gave a value of 14 units (normal, 4 units), and the reaction to Neefe and Reinhold's [7] cephalin-cholesterol flocculation test was graded 2 (on a basis of 1 to 4, in which 1 represents the weakest and 4 the strongest reaction).

TABLE 2.—*Values for Fat and Nitrogen in the Stool of a Child with Chronic Relapsing Pancreatitis and Hyperlipemia* *

Diet	Total Solids, Gm.	Fat †			Nitrogen ‡	
		Total, Gm.	Per Cent of Dry Weight	Per Cent of Fat Ingested	Total, Gm.	Per Cent of Nitrogen Ingested
High fat §.....	13.5	1.47	10.9	2.0	1.45	13.9
Elective ‖.....	17.0	2.2	12.9	3.5	1.40	10.5
Low fat ¶.....	21.5	2.1	9.8	8.4	1.5	8.2

* Each determination was made on a seventy-two hour specimen, except for the one made between May 1 and 5, 1947 for which a ninety-six hour specimen was used. Values reported are the average for twenty-four hours.

† Fat was determined according to the method of Saxon (J. Biol. Chem. **17**:99-102, 1914).

‡ The Kjeldahl method was used in this determination.

§ Calories, 1,580; fat, 74 Gm.; protein, 65 Gm., and carbohydrate, 163 Gm. (April 17 to 20).

‖ Calories, 1,805; fat, 62 Gm.; protein, 83 Gm.; carbohydrate, 222 Gm. (May 1 to 5).

¶ Calories, 2,070; fat, 25 Gm.; protein, 114 Gm.; carbohydrate, 347 Gm. (May 11 to 13).

3. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399-414 (Sept.) 1938.

4. Cherry, I. S., and Crandall, L. A., Jr.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, Am. J. Physiol. **100**:266-273 (April) 1932.

5. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53-73 (April) 1928; The Determination of Cholesterol in Blood, ibid. **24**:227-231 (March) 1916. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, ibid. **27**:107-112 (Oct.) 1916. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism, J. Lab. & Clin. Med. **16**:158-166 (Nov.) 1930.

6. Maclagan, N. F.: The Thymol Turbidity Test: New Indicator of Liver Dysfunction, Brit. J. Exper. Path. **25**:234-241 (Dec.) 1944.

7. Neefe, J. R., and Reinhold, J. G.: Laboratory Aids in the Diagnosis and Management of Infectious (Epidemic) Hepatitis, Gastroenterology **7**:393-413 (Oct.) 1946. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261-269 (May) 1939.

Additional studies showed good utilization of dietary fats and proteins (table 2). The values for duodenal diastase [8] and trypsin [9] were within normal limits but that for lipase was slightly decreased (table 3).

After ingestion of a diet with a low content of fat (25 Gm.), the value for the total lipid content of the blood was found to be decreased; however, this decrease was not due primarily to the low ingestion of fat because the levels began to decrease before the child was placed on the low fat diet. The lowest level reached was still about three times normal (table 1).

During his first visit to the hospital after his admission to the clinic, the boy did not experience any abdominal discomfort. Two months after his first admission, he again complained of cramping epigastric pain. This was accompanied with vomiting and drowsiness. There was no elevation in temperature. At the time of his second admission, four or five hours after the onset of this attack, he was still drowsy and there was exquisite tenderness in the upper part of the abdomen, which was maximal on the left. Spasm of the abdominal musculature in this region

TABLE 3.—*Values for Duodenal Enzymes in a Child with Chronic Relapsing Pancreatitis and Hyperlipemia*

Samples Taken 4/28/47	* p_H	Diastase, Gm. of Maltose per Cc.*	Trypsin, Cc. of N/10 KOH †	Lipase, Cc. of N/20 KOH ‡
1.....	7.2	1.0	...	8.0
2.....	6.8	0.5	1.1	36.0
Normal values, average §.....	6.89	1.015	1.51	83.0

* Nørby method.[8]
† Method of Willstätter and associates modified by Hammarsten, Ågren and Lagerlöf.[9b]
‡ Maclay's (Am. J. Tech. Methods **14**: 197-201 [July] 1948) modification of Cherry and Crandall's method [4] was used.
§ Normal values for adults as given by Comfort and Osterberg (Gastroenterology **4**: 85-91 [Jan.] 1945).

was graded 3 (on a basis of 1 to 4, in which 1 represents the least and 4 the greatest spasm). The spleen was again palpable. The leukocyte count was 12,200. Eighty-six per cent of the leukocytes were polymorphonuclear. The sedimentation rate was 63 mm. in one hour. Values for serum amylase and serum lipase were definitely elevated, as were those for blood lipids (table 1). Values for the fatty acids in the blood at the time of the second admission were not quite so high as at the time of the first admission. There was little change in the values for cholesterol and phospholipids (table 1). The child was treated conservatively with an infusion of a solution of glucose and with daily intramuscular injections of 160,000 units of penicillin.

On the day following admission, the boy's condition was improved. He was alert, and there was less abdominal tenderness and spasm. Slight abdominal pain recurred once during the remainder of his stay in the hospital.

8. Nørby, cited by Lagerlöf.[12]

9. (*a*) Willstätter, R.; Waldschmidt-Leitz, E.; Duñaiturria, S., and Künstner, G.: Ueber Pankreasenzyme: Zur Kenntnis des Trypsins, Ztschr. f. physiol. Chem. **161**:191-209, 1926. (*b*) Hammarsten, E.; Ågren, G., and Lagerlöf, H.: The Correlation Between Secretin Dose and Pancreatic Effect in Man, Acta med. Scandinav. **92**:256-266, 1937.

PANCREATITIS IN CHILDREN

Review of the literature showed that prior to 1943 only 26 reports of cases of pancreatitis in children were published. In 1932, Foged [10] collected reports of only 10 cases of children from a total of 1,510 reports of cases of acute pancreatitis which he reviewed. Secondary pancreatitis, as is well known, may complicate certain common diseases such as scarlet fever, diphtheria and parotitis. Reports of only 2 cases of chronic pancreatitis in children were found in the literature. These were the 2 cases included in the series reported by Comfort and his co-workers [1] in 1946.

The manifestations of acute pancreatitis in children are striking. Sudden onset of severe abdominal pain is the most frequent symptom. Repeated vomiting is usually associated with the pain, which is characteristically located in the upper part of the abdomen. There is generalized abdominal tenderness. The clinical picture resembles that of shock. However, according to Dobbs,[11] cyanosis of the face and bluish discoloration of the external abdominal wall, which suggest the diagnosis of acute pancreatitis in adults, do not occur in children. There is always a decided elevation in the values for serum lipase and serum amylase. Glycosuria and hyperglycemia may occur. No report has been found of hyperlipemia occurring simultaneously with acute pancreatitis in a child.

According to the literature, chronic relapsing pancreatitis appears to consist of recurring exacerbations of acute pancreatitis, separated by short or long intervals of relative clinical quiescence. It is said to be manifested by recurring attacks of severe pain in the upper part of the abdomen which last for days, during which glycosuria, hyperglycemia and steatorrhea may appear. There may be disturbance of pancreatic function as indicated by an abnormal response to the secretin test.[12] Values for serum amylase and lipase may be elevated with each attack. The sedimentation rate may also be prolonged. Roentgenologic demonstration of pancreatic calculi and the finding of excessive amounts of fat and nitrogen in the stools substantiate the diagnosis.

LIPEMIA IN CHILDREN

Lipemia may occur in children in various conditions, the commonest of which are diabetes mellitus and nephrosis. It may occur in hepatic disease when there is impairment of the internal utilization of fat. In patients with low basal metabolic rates, such as result from hypothyroidism, lipemia with high values for blood cholesterol results. Certain blood dyscrasias, such as acute and chronic anemias, leukemia and purpura fulminans, may be associated with varying degrees of lipemia. Starvation has been known to cause an increase in blood lipids. The lipidoses, including glycogenosis (von Gierke's disease), Niemann-Pick disease and the xanthomatoses, are usually associated with an increase

10. Foged, J.: Pankreasapoplexie bei einem Kinde, Zentralbl. f. Chir. **59**: 2161-2163 (Sept. 3) 1932.

11. Dobbs, R. H.: Acute Pancreatitis in Childhood, Lancet **2**:989-991 (Nov. 2) 1935.

12. Lagerlöf, H. O.: Pancreatic Function and Pancreatic Disease Studied by Means of Secretin, translated by H. D. Frey, New York, The Macmillan Company, 1942.

in the various blood lipids. One case of severe lipemia in pituitary diabetes [13] has been reported.

The only conditions in which lipemia occurs that are of special interest in connection with the present case are pancreatic disease and idiopathic hyperlipemia.

Thannhauser, in his extensive study of the lipidoses, described an entity which he called "idiopathic hyperlipemia with hepatosplenomegaly and secondary xanthomatosis" and included 6 cases which had been reported.[14] Reports of 2 additional cases [15] have been found, making a total of only 8 such cases. All these cases were of children. Cases reported separately by Opitz [14b] and by Holt and associates [14d] were the only ones in which abdominal symptoms similar to those in ours occurred.

Opitz' case was that of a boy, aged 12 years, who had severe recurrent attacks of left-sided abdominal pain associated with shocklike symptoms from the time that he was 5 years old. Physically, he was underdeveloped for his age. His scleras were yellow, but there was no elevation of his serum bilirubin level. His appetite was good, but he had a definite intolerance to fatty foods. There were no cutaneous lesions resembling xanthomas. His liver and spleen were enlarged. The serum lipid level was reported to vary between 1,800 and 2,226 mg. per hundred cubic centimeters. The cause of the abdominal attacks was not discovered, as the child was not operated on. Opitz did not indicate that in his opinion the abdominal pain and the hyperlipemia were related.

The case reported by Holt and his co-workers was that of a girl, aged 11 years, who had had periodic attacks of abdominal pain, associated with projectile vomiting, abdominal rigidity, fever, leukocytosis and shock, from the time she was 4 years old. The child had psoriasis and peculiar ulcerated cutaneous lesions resembling those of xanthomatosis. There was hepatosplenomegaly and keloid formation in an abdominal scar. She had pronounced hyperlipemia, due primarily to increase in neutral fat. The value for total serum lipids ranged from

13. dell'Acqua, G.: Pituitary Diabetes with Severe Lipemia, Med. Klin. **39**:499 (July 9) 1943.

14. (*a*) Bürger, M., and Grütz, O.: Ueber hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut, Arch. f. Dermat. u. Syph. **166**:542-575 (Oct.) 1932. (*b*) Opitz, H.: Hochgradige Lipämie unklarer Genese bei einem 12 jährigen Knaben, Deutsche med. Wchnschr. **1**:88-89 (Jan. 18) 1935. (*c*) Franklin, S., and Avery, H.: Splenomegaly with Lipæmia, Proc. Roy. Soc. Med. **30**:711 (April) 1937. (*d*) Holt, L. E., Jr.; Aylward, F. X., and Timbres, H. G.: Idiopathic Familial Lipemia, Bull. Johns Hopkins Hosp. **64**:279-314 (May) 1939. (*e*) Bernstein, S. S.; Williams, H. H.; Hummel, F. C.; Shepherd, M. L., and Erickson, B. N.: Metabolic Observations on a Child with Essential Hyperlipemia, J. Pediat. **14**:570-580 (May) 1939. (*f*) Goodman, M.; Schuman, H., and Goodman, S.: Idiopathic Lipemia with Secondary Xanthomatosis, Hepatosplenomegaly and Lipemic Retinalis, ibid. **16**:596-606 (May) 1940.

15. Abegg, W.: Ein Fall von hochgradiger alimentärer "hepatogener" Fettretention im Blut bei einem 11 jährigen Kinde, Jahrb. f. Kinderh. **149**:94-107, 1937. Herbert, F. K.: Case of Juvenile Xanthomatosis, with Enlarged Liver and Spleen and Greatly Increased Plasma Lipoids, Arch. Dis. Childhood **18**:41-49 (March) 1943.

1,420 to 8,200 mg. per hundred cubic centimeters. An investigation of the family revealed that five of the eight members had blood lipid values of more than 1,000 mg. per hundred cubic centimeters. The onset of the patient's pain was observed to follow a gradual rise in blood lipids to a critical level of 8,000 mg. per hundred cubic centimeters. When the blood fat exceeded this figure, an attack ensued within a few hours. Following the onset of the attack, there was a rapid reduction of blood lipids. The liver and spleen seemed to become larger during each attack, receding to their original size two weeks after the attack. Lipemia retinalis was present but disappeared twenty-four hours after the onset of an attack and returned about two weeks afterward, at which time the blood lipids had reached the level of approximately 6,000 mg. per hundred cubic centimeters.

Holt concluded that the cause of the colicky pain was the acute distention of the capsules of the liver and spleen, caused by the presence of fat which they had removed from the blood when the total lipids reached the critical level. This was not verified by biopsy of tissue from the spleen or liver. The child was operated on only once and that was at the time of her first attack at the age of 4 years. At that time, the pancreas was not examined, but because of the lack of positive findings in the explored region, the diagnosis of acute pancreatitis was made in retrospect. An extensive study was made on this patient of the effect of treatment with lecithin, choline, thyroxin U. S. P., insulin, lipocaic and extract of the anterior lobe of the pituitary. The patient's condition remained unimproved. The attacks were controlled by giving her a diet that contained little fat. The lowest blood lipid level was reached after a series of transfusions.

CHRONIC PANCREATITIS AND HYPERLIPEMIA

The coexistence of pancreatitis and hyperlipemia is not common, even in adults. Speck [16] in 1846 was probably the first to describe the clinical condition of lipemia and attacks of colicky pain. Thannhauser included 10 cases of pancreatitis with hyperlipemia in his series classified as "hyperlipemia with secondary xanthomatosis in chronic pancreatitis." None of these patients was children. The history in the cases reported by Joël [17] and Wijnhausen [18] was quite similar to that in our case.

The patient described by Joël was a man 29 years of age. He had recurrent attacks of severe upper abdominal pain starting four weeks after trauma to his abdomen. There was vomiting, but no fever, with each attack. The attacks occurred at intervals of several months. There were short and long periods of relative clinical quiescence between attacks. The lipemia was demonstrated seven weeks after the onset of the colicky pain. Values for neutral fat and for cholesterol were ten times normal. The response of the pancreas to the secretin test was normal. There were normal amounts of fecal fat and fecal nitrogen. There was no glycosuria or hyperglycemia. A diagnosis of acute and chronic pancreatitis was made.

16. Speck, C.: Ein Fall von Lipämie, Arch. d. Ver. f. wissensch. Heilk, 1846, pp. 232-238.

17. Joël, E.: Zur Klinik der Lipämie, Ztschr. f. klin. Med. **100**:46-60, 1924.

18. Wijnhausen, O. J.: Ueber Xanthomatose in einem Falle rezidivierender Pankreatitis, Berl. klin. Wchnschr. **58**:1268-1270 (Oct. 24) 1921.

Wijnhausen's patient was a man, 35 years old, who for ten years had recurrent attacks of abdominal pain following severe trauma to the abdomen. Nausea, vomiting, glycosuria and fever occurred with each attack, which lasted approximately two days and occurred at intervals of one to two months. Xanthomatous cutaneous lesions had developed about a year after the first attack. These lesions became more prominent at the time of an attack and receded afterward. Operation revealed that the pancreas was swollen, tense and firm. There was a mass attached to it which contained necrotic tissue filled with crystals of fatty acids. After drainage of the pancreas, the patient recovered but continued to have recurrent attacks of pain. However, he responded favorably when given a low fat diet.

COMMENT

The patient in the present report exhibited many of the characteristics of both idiopathic hyperlipemia and chronic pancreatitis with hyperlipemia. The features characteristic of idiopathic hyperlipemia were (1) a family history of xanthomatosis, (2) xanthomatous lesions which disappeared when the patient was on a fat-free diet, (3) keloid formation in the abdominal scar, (4) hepatosplenomegaly, (5) chylous serum, (6) pronounced hyperlipemia, with fatty acid values ten times normal and (7) decrease in degree of lipemia following attacks of abdominal pain.

The features characteristic of chronic pancreatitis with hyperlipemia which were observed in our patient were (1) seven severe attacks of abdominal pain, each lasting for days, since the patient was 4 years of age, (2) ruptured abscesses of the pancreas observed on operation on three occasions, (3) periods of relative clinical quiescence, (4) a few attacks precipitated by trauma, (5) glycosuria during one attack, (6) elevation of serum amylase and serum lipase levels, (7) slight impairment of pancreatic function, (8) leukocytosis at time of attack and (9) increased sedimentation rate at the time of an attack.

The diagnosis of chronic relapsing pancreatitis with hyperlipemia appears warranted in the case we have reported. The cases reported by Opitz and by Holt and associates were probably examples of the same clinical entity. Our case is the first one in which there appears to be an adequate explanation for the recurrent abdominal symptoms. Further investigation is necessary to determine the relationship between relapsing pancreatitis and hyperlipemia.

SUMMARY

A case of chronic relapsing pancreatitis associated with decided hyperlipemia in a boy 8 years old is reported. A review of the literature indicated that the incidence of acute pancreatitis and chronic relapsing pancreatitis in children is low, and a report of acute pancreatitis or chronic pancreatitis associated with hyperlipemia in a child was not found. The occurrence of lipemia in pathologic conditions, with special reference to its presence in "idiopathic hyperlipemia" and in pancreatic disease, is discussed. Of the 8 cases of idiopathic hyperlipemia occurring in children which have been reported in the literature, 2 were reviewed in detail because of the similarity between them and the case reported herein. Our patient demonstrated characteristics of both idiopathic hyperlipemia and chronic relapsing pancreatitis.

The Mayo Clinic.

WERNICKE'S SYNDROME DUE TO VITAMIN B DEFICIENCY

Report of the Disease in Two Infants

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MANILA, PHILIPPINE ISLANDS

IN 1881, Wernicke [1] described a syndrome characterized by drowsiness or stupor, ophthalmoplegia and ataxia and reported his pathologic observations. He attributed the condition to the toxic effect of a variety of substances or poisons. Since then, many of the cases of this syndrome have been seen in alcoholic persons, for which reason it came to be accepted as one of the serious manifestations of chronic alcoholism, or at least as one of its complications.

In recent years, however, cases have been described in the literature in nonalcoholic persons. Bowman and Wortis [2] had collected 40 cases from the literature up to 1941. Campbell and Biggart [3] also reported cases of Wernicke's syndrome in conditions other than alcoholism. Of their 12 cases only 1 included signs of frank alcoholism. They observed that diseases accompanied by malnutrition, such as gastrointestinal conditions, tuberculosis, anorexia and hyperemesis gravidarum, can give rise to the syndrome. Ecker and Woltman [4] reported a case in which evidence of thiamine deficiency was present. The association of peripheral neuropathy, and even of degenerative changes of the posterior columns of the spinal cord, with Wernicke's syndrome in man pointed to the probable nutritional nature of the disease and made a deficiency in one or more of the vitamins a likely cause. Campbell and Russell [5] suggested that deficiencies in thiamine and nicotinic acid were causative factors.

There is strong experimental evidence that the syndrome is caused by a severe thiamine deficiency and that the clinical manifestations respond promptly to administration of thiamine. The symptoms and anatomic lesions of Wernicke's syndrome have been reproduced experi-

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1. Wernicke, K.: Lehrbuch der Gehirnkrankheiten, für Aerzte und Studierende, Berlin, T. Fischer, 1881, vol. 2, pp. 229-242; cited by Zimmerman.[6a]

2. Bowman, K. M., and Wortis, H.: Psychiatric Syndromes Caused by Nutritional Deficiency, A. Research Nerv. & Ment. Dis., Proc. (1941) **22**:168, 1943.

3. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy: Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. **48**:245, 1940.

4. Ecker, A. D., and Woltman, H. W.: Is Nutritional Deficiency the Basis of Wernicke's Disease? Report of Case, J. A. M. A. **112**:1794 (May 6) 1939.

5. Campbell, A. C. P., and Russell, W. R.: Wernicke's Encephalopathy, Quart. J. Med. **10**:41, 1941.

mentally in animals [6] (pigeon, rat, dog and fox) fed a thiamine-deficient diet and they correspond with those observed in man. Thus, in the opinion of most workers today, this syndrome is directly caused by a deficiency of thiamine and possibly of some other member of the B complex. Its occurrence in alcoholic persons is stated to be the result of the thiamine deficiency which is often present in chronic alcoholism and, thus, the syndrome is related to Korsakoff's psychosis.

The location of the lesions in the nervous system in Wernicke's syndrome is so uniform and constant that it constitutes one of the remarkable features of this disease. According to Zimmerman [6a] the lesions involve

> . . . the paraventricular gray matter of the 3rd ventricle, the mamillary bodies, the periaqueductal region where the 3rd and 4th cranial nerve nuclei reside, the corpora quadrigemina and the region beneath the ependyma lining the floor of the 4th ventricle. Lesions in the latter locations are apt to implicate some of the cranial nerve nuclei. In the early stages, the macroscopic appearance of these lesions is distinctly hemorrhagic, but, with increasing age, they assume a rusty brownish color.

Because of the hemorrhagic nature of the lesions and the predilection for the gray matter in the sites mentioned, this disease is now known as "superior hemorrhagic polioencephalopathy due to lack of vitamin B complex." [7] Bowman and Wortis [2] reported clinical findings in 34 cases of Wernicke's syndrome, 31 of which occurred in persons with chronic alcoholism. Their observations are quoted here because they summarize present day knowledge of the disease:

1. The syndrome as originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system and needs not necessarily be complete in any case.

2. The results obtained indicated that: (a) the ophthalmoplegia responds to thiamin therapy; (b) the clouding of consciousness may be related to anything which interferes with the proper brain metabolism. Among the known offenders are: lack of carbohydrate, lack of oxygen, lack of thiamin, nicotinic acid and riboflavin; and probably lack of many other substances now under investigation; (c) the ataxia is difficult to evaluate and its response to therapy has not as yet been worked out.

3. Other deficiency syndromes (pellagra, nicotinic acid deficiency encephalopathy, riboflavin deficiency, scurvy) may and do superimpose themselves on the more usual Wernicke picture; and these require specific treatment.

4. The ophthalmoplegia is almost invariably preceded or accompanied by peripheral neuropathy. Since the latter is associated with a thiamin deficiency, this finding tends to confirm Alexander's thesis that they have a common etiology and that the polioencephalopathic changes represent a more complete deficiency in thiamin.

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6. (*a*) Zimmerman, H. M.: Pathology of Vitamin B Group Deficiencies, A. Research Nerv. & Ment. Dis., Proc. (1941) **22**:51, 1943. (*b*) Alexander, L.; Pijoan, M., and Myerson, A.: Beri-Beri and Scurvy: Experimental Study, Tr. Am. Neurol. A. **64**:135, 1938; cited by Bowman and Wortis.[2] (*c*) Alexander, L.: Wernicke's Disease, Am. J. Path. **16**:61, 1940; cited by Bowman and Wortis.[2]

7. Jordan, E. P.: Standard Nomenclature of Disease and Standard Nomenclature of Operations, ed. 3, Chicago, American Medical Association, 1942.

5. Delirium, with its marked increase in psychomotor activity, and hence in total metabolism, usually precedes the development of this syndrome. In this type of case, the early administration of thiamin will prevent the development of ophthalmoplegia.

6. All patients who received adequate vitamin therapy recovered. In the recovered cases, the development of a Korsakoff syndrome is the rule. The latter does not show a consistent response to thiamin therapy as has frequently been asserted.

To support these conclusions, these same authors studied the blood level of pyruvates in their patients and observed that in 11 of them the pyruvate level of the blood on fasting was elevated and returned to normal rapidly after vitamin B therapy. This fall in pyruvic acid content was associated with rapid clinical improvement of the patient.

Eddy and Dalldorf [8] stated that Wernicke's syndrome was observed in breast-fed infants in Japan. This is the only direct reference to Wernicke's syndrome in infants which I have seen so far. The references almost invariably are to reports on adults, most of whom had chronic alcoholism. For this reason I consider it interesting to report the cases of 2 infants who presented all the characteristics of Wernicke's syndrome and who responded dramatically to vitamin B therapy.

REPORT OF CASES

CASE 1.—E. M., a Filipino girl, 1 year and 4 months old, was admitted to the pediatric service on May 24, 1946 because of extreme bodily weakness and lethargy. According to the mother, three weeks before her admission the child had a cough which was more frequent during the day and which sometimes provoked vomiting of mucoid whitish material. Three days afterward, there was a moderately high, continuous fever which lasted several days and which subsided without treatment. During this period, the child had bleeding from the nose on two occasions, a few drops of blood each time. One week after the onset of the cough the mother noticed running of the nose and the reappearance of fever, which was low with intermittent rising in the afternoon and accompanied with profuse sweating. This condition continued for about a week. After this, that is, one week before her admission, the child lost her appetite, and the mother noticed a gradual loss of muscular strength, so that the child could not stand up alone, although she had begun to walk before the onset of the illness. This weakness increased until the child could not hold her head up. Somnolence was noticed shortly before her admission. The eyelids drooped, and there was squinting of the eyes.

The past history was noncontributory. The mother had at the time a chronic cough for more than a month, which was accompanied with fever and sweating at night. Physical examination of the mother failed to detect definite signs of active tuberculosis. The dietetic history was significant. The child was still breast fed at the time of her admission and received no other kind of milk. She had been eating rice gruel, rice water (*am*) and a few other accessory foods since the age of 7 months. No vitamin preparations were given.

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8. Eddy, W. H., and Dalldorf, G.: The Avitaminoses: The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases, ed. 3, Baltimore, Williams & Wilkins Company, 1944, pp. 211-212.

On her admission to the hospital the child was noted to be poorly nourished, although fairly well developed. She was apathetic, irritable and prostrated, and the left eye deviated inward. The anterior fontanel, which was still open (the size of a dime), was soft and depressed. The eyelids were drooping, the left more than the right. The head hung forward and moved freely from side to side with changes in position of the trunk. It was evident that she could not raise her head (head drop). The voice, although not exactly aphonic, was weak and sounded distant when she cried, reminiscent of the aphonia of infantile beriberi. Auscultation revealed a few sonorous and moist rales on both sides of the chest. The lower extremities dangled helplessly, but a little voluntary movement could be observed in the right leg. Sensation to pinprick seemed normal. The knee jerk was weak and sluggish on both sides, especially the right. Other reflexes were normal. The eyes showed paralysis of the left lateral rectus muscle with inward deviation.

Laboratory examinations showed a hemoglobin content of 75 per cent; red blood cells numbered 4,050,000 and white blood cells, 11,850, with a differential count of 73 polymorphonuclear leukocytes, 25 lymphocytes, 1 monocyte and 1 eosinophil. The urine was normal in all respects. The stools showed ova of Ascaris (1 plus). A Pandy test on the cerebrospinal fluid showed a faintly positive reaction. Glucose measured 71.4 mg. per hundred cubic centimeters. The fluid contained 4 lymphocytes per cubic millimeter. Fluoroscopic examination revealed a slight prominence of the right hilar shadow.

The child had been referred from the dispensary with the diagnosis of encephalitis or possible poliomyelitis. Clinically, she presented the symptoms of encephalitis, with lethargy, ophthalmoplegia and a slight nystagmus observed on one occasion. On examination, however, the cerebrospinal fluid was normal, and the head drop and extreme weakness of the extremities with loss of reflexes suggested polyneuritis. Although this baby was past the age in which infantile beriberi is usually seen, the polyneuropathy and pronounced anorexia made me suspect a thiamine deficiency. The normality of the spinal fluid excluded the possibility of inflammatory processes, such as encephalomyelitis. Guillain-Barré albuminocytologic dissociation was evidently absent. Five milligrams of thiamine hydrochloride U. S. P. was given hypodermically daily. After the second injection, the child woke up from her lethargy and became more active, even playful. The appetite reappeared almost suddenly. Hydrolyzed yeast powder (basamin®) was added to the milk formula, 1 heaping tablespoonful (approximately 15 cc.) four times daily. The drooping eyelids opened; the squint disappeared; the neck muscles recovered their power, and the child began to raise her head. After the sixth injection of thiamine hydrochloride, the treatment was continued with vitamin B complex tablets (blexin®) in addition to the hydrolyzed yeast. The lower extremities gradually became stronger, and the child was able to walk again one week after the beginning of treatment, although the muscles were still flabby and weaker than normal. The resident physician remarked that the addition of the vitamin B complex preparation had hastened the return of muscular strength so that the child began to stand up soon after the institutional therapy. The reflexes returned; the weight increased by 1 kilogram during her stay in the service. She was discharged June 11, fully recovered from the complaint for which she had been admitted, although she was still underweight.

Readmission.—On August 13 next, she was readmitted because of acute bronchitis and was noted to be still undernourished. The knee jerk was again absent on both sides. Sulfamerazine, thiamine hydrochloride (5 mg. hypoder-

mically daily) and hexylresorcinol crystoids® for the ascariasis constituted the treatment besides the diet. The reaction to a Vollmer® patch test for tuberculosis was slightly positive (1 plus) after forty-eight hours and negative after seventy-two hours. A roentgenogram of the chest failed to show any evidence of tuberculosis. The child improved rapidly, and the respiratory infection was controlled in one week. The knee jerk returned on the sixth day in the hospital. The weight increased. She was discharged on August 21, fully recovered from the bronchitis and without any apparent signs of thiamine deficiency, aside from a certain amount of muscular weakness.

On August 24 the patient was brought to the hospital and presented before a staff conference. Three days later, that is, on August 27, the baby was brought to the hospital once more, this time with high fever, cough and dyspnea. The new illness had begun suddenly the day after she had left the hospital. Examination of the chest revealed dulness over the base of the right lung, diminished breath sounds and increased vocal fremitus over the same area, with a few fine crepitant rales at the level of the eighth and tenth thoracic vertebrae. Examination of the blood showed leukocytosis (39,500 cells), with 78 per cent polymorphonuclear forms, of which 16 per cent were stab cells and 22 per cent lymphocytes, with no mononuclear cells or eosinophils. The diagnosis of lobar pneumonia was confirmed by the results of roentgenologic examination. The knee jerk was present on both sides, although a little weaker than normal. Administration of sulfamerazine brought the temperature down to normal in twenty-four hours, and the child was discharged August 31, in frank convalescence. I have lost track of her since then.

This infant undoubtedly had polioencephalopathy and manifested the clinical criteria of Wernicke's syndrome, i. e., drowsiness, ophthalmoplegia and ataxia. The extreme loss of muscular power in the extremities and neck with loss of reflexes, the pronounced anorexia and partial aphonia were suggestive of a severe thiamine deficiency. The rapid response to relatively small doses of thiamine tends to prove this.

CASE 2.—B. C., a 10 month old Filipino girl, was admitted to the pediatric service on June 21, 1948, with the chief complaint of vomiting and strabismus of five days' duration. The present illness apparently started in the first week of June as loose, watery bowel movements, occurring five to six times a day. There was mucus but no blood, and the stools were greenish yellow. From the beginning of the disease, the baby vomited the milk previously taken once in a while. The diarrhea and occasional vomiting continued for several days in spite of treatment in a puericulture center and by a private physician. The diarrhea was apparently controlled but the vomiting continued. Eight days before her admission, vomiting stopped, but the mother noticed that the child had a fever which was especially high at night. Under treatment, the fever disappeared, but the occasional vomiting continued. On June 16, after high fever, the mother first noticed squinting of the eyes and movements of the head from side to side. Since then, the child had low grade fever, especially in the afternoons and at night. A physician was again consulted, and he advised hospitalization.

This child, the second of two children, was born full term, spontaneously, without evidence of injury at birth. Feeding had been by breast up to the time of her admission with no definite intervals between, or times for feedings. At 6 months, sweetened condensed milk, 1 tablespoonful (15 cc.) with 4 ounces (118 cc.) of water was given as a supplemental feeding when the mother had to

go out. The condensed milk feedings were discontinued last March. A vitamin B preparation benerva® syrup and halibut liver oil had been given since the early months of life. The vitamin preparation was stopped in March also. The halibut liver oil was given up to her present admission. Orange juice and, occasionally, potato purée, rice gruel and bananas were given. Development had been normal. At 9 months, the child stood up supporting herself. The child was admitted to the Philippine General Hospital in March 1948, because of bronchopneumonia. She was discharged after a week as recovered.

Physical examination showed a well developed, but poorly nourished, somnolent, weak, irritable child, weighing only 14 pounds 7 ounces (6,549 Gm.). Her height was 28 inches (71 cm.). The significant findings were as follows: The right eyelid was slightly ptosed. The right eye had an internal squint. There was no nystagmus. The pupils, 3 to 4 mm. in diameter, reacted to light sluggishly. The child's facies showed somnolence and absence of expression. In the chest, there were slight dulness and diminution of breath sounds over the base of the right lung. The heart did not show evidence of enlargement. The muscles were flabby and extremely weak. The child lay practically immobile with the extremities flaccid. The Kernig, Brudzinski and Babinski signs and the tache cérébrale were not present. Plantar flexion was sluggish. The knee jerk was present but weak and almost absent on the left. The abdominal reflexes and the grasping reflex were absent. Examination of the spinal fluid on June 22 showed 2 lymphocytes per cubic millimeter. The reactions to the Pandy and Levinson tests were negative. By the five tube method, sugar measured 40 to 50 mg. per hundred cubic centimeters. Chlorides were 759 mg. per hundred cubic centimeters. The fluid showed no micro-organisms, and cultures yielded no pathogens. Examinations of the blood, stool and urine showed no abnormality. The fundi were normal. The reaction to the Mantoux test (with 1:1,000 old tuberculin) was 2 plus. A roentgenogram of the lungs showed a primary tuberculous infection.

The diagnosis on her admission was acute encephalitis, but one of the physicians remarked that there seemed to be hypersensitiveness at the point of exit of the facial and supraorbital nerves and suggested the possibility of tuberculous meningitis before the cerebropsinal fluid findings were known. With the normal cerebrospinal fluid, I at once recalled the first child with Wernicke's syndrome, since she also had had somnolence, strabismus, slight ptosis of the eyelid and severe muscular weakness. The only treatment given was 100 mg. of thiamine hydrochloride, hypodermically. The original dose ordered had been 10 mg., but, through a misunderstanding, the intern actually gave 100 mg. On the next morning, there was no strabismus, the child was less irritable, and the grasping reflex reappeared on both sides, on the left stronger than on the right. No thiamine hydrochloride was given for the next three days, but the improvement continued during that period. The knee jerk became positive on both sides, although the left remained weaker than its fellow. The injections of thiamine were continued, 10 mg. daily hypodermically. Five days after her admission, the baby had improved so much that she was practically normal. There was no more tendency to somnolence; she cried more vigorously and could recognize the mother and even smiled at the intern in charge.

The child remained in the service until July 6, a total of fifteen days. During that period the treatment consisted of administration of thiamine hydrochloride and, later, a preparation containing vitamins of the B complex and the proper diet. During the latter part of her stay in the service, as she grew better the symptoms of tuberculosis became more evident, with the appearance of low grade fever and

cough. Occasional rales were heard on auscultation. Accordingly, colloidal copper morrhuate (gadusan®) was given by the hypodermic route. The baby was finally discharged without any of the manifestations of thiamine deficiency but still slightly undernourished.

COMMENT

In this second infant the signs of profound thiamine deficiency apparently developed as a result of the diarrhea and vomiting. The disease in the first infant, however, began with an infection of the upper respiratory tract. The history of the feeding shows that in contrast to the first baby, this child had been breast fed but, at the same time, had received sweetened condensed milk rather irregularly. However, these supplemental feedings had been discontinued two months before the present illness. The history also showed that this baby had been receiving thiamine in the form of benerva® syrup which was also stopped two months before the present illness. It is clear that the feeding of this baby left much to be desired, and that the food intake during the long-continued diarrhea and during the secondary infection which began one week before her admission must have been sharply curtailed.

In these 2 cases of Wernicke's syndrome, therefore, it is seen that the pseudoencephalitic manifestions occurred in infants past the age of incidence of infantile beriberi. In both, the feeding had been unsatisfactory with regard to quantity and quality, leading to a state of chronic thiamine deficiency. In both, the symptoms of acute thiamine deficiency occurred in the course of a febrile infection which probably acted as the trigger mechanism. One had an infection of the upper respiratory tract, while the other had an infection of the upper respiratory tract as a complication of diarrhea which was probably of alimentary origin. In both of them, the administration of thiamine produced a dramatic improvement of the symptoms leading to recovery.

One may well ask whether Wernicke's syndrome is also a part of the clinical picture of infantile beriberi. Kato,[9] in an article based principally on reports in the Japanese literature, mentioned somnolence, apathy, extreme muscular weakness and involvement of the cranial nerves, with ptosis and aphonia as the commonest manifestations. But these signs of beriberi are not observed in the Philippines, except the aphonia. Guerrero and Quintos,[10] Albert [11] and others failed to report these manifestations at a time when infantile beriberi in its severest and most malignant forms was of daily occurrence in Manila. Albert mentioned head drop as a manifestation of infantile beriberi, but some of his co-workers were inclined to attribute this symptom to the malnutrition rather than to the thiamine deficiency. Eddy and Dalldorf [8] stated that Wernicke's syndrome has not been reported as a complication of oriental beriberi, although they also refer to Campbell and Biggart [3] as citing Tanaka as authority for the statement that the syndrome has been observed in breast-fed infants in Japan.

9. Kato, K.: Beriberi in Infancy and Childhood, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 35, pp. 11-12.

10. Guerrero, M. S., and Quintos, J.: El beriberi en los niños de pecho, Manila, L. Cribe, 1910.

11. Albert, J.: Studies on Infantile Beriberi Based on Five Hundred and Fourteen Cases, Philippine J. Sc. **45**:297, 1931.

More recently, Spillane (1947) [12] also cited Tanaka, after commenting on the fact that Wernicke's syndrome has not been described in the literature on Oriental beriberi. This author stated that, in 1934, Tanaka concluded that the so-called breast milk intoxication in Japanese infants was identical with Wernicke's encephalopathy. As Fehily [13] observed, and as is well known among Filipino pediatricians, the Japanese school has long been of the opinion that the clinical picture of infantile beriberi is partly the result of intoxication through toxic substances found in the milk of beriberic mothers. Several Japanese authors considered the encephalopathy to be a cerebral form of infantile beriberi, while others stated it to be a different entity. Tanaka reported signs of brain stem lesions in these babies, in addition to gastrointestinal symptoms and manifestations of a general cerebral disorder. Oculomotor paralysis, ocular palsies, nystagmus, choreoathetoid movements, ataxia and opisthotonos were quite commonly observed. In most patients, the knee jerk reflexes were reduced. One infant revealed on autopsy the lesions of Wernicke's encephalopathy. At any rate, the present patients did not present the clinical picture of infantile beriberi as it is seen in the Philippine Islands.

The observation of the resident physician that improvement was more rapid after the inclusion of a vitamin B complex preparation in the treatment may be taken as supporting the conclusion of Bowman and Wortis, that, while the ophthalmoplegia responds quickly to thiamine therapy, the ataxia is less clearly influenced by administration of pure thiamine and that the clouding of consciousness is the result of a variety of factors, any of which interferes with proper cerebral metabolism. In these patients the sensorium cleared after the administration of about 10 mg. of thiamine, even before the ophthalmoplegia improved.

The etiologic basis in these present patients must have been the long-standing erroneous diet. The one infant had no gastrointestinal disturbance. There was no positive evidence of active tuberculosis, although the mother was suspected of being tuberculous. The anorexia, as far as could be determined, accompanied the appearance of the syndrome instead of preceding it. The only plausible factor was the faulty diet. The infant was breast fed and had not been weaned in spite of her age (16 months). The accessory foods given were almost purely of carbohydrate nature and no cow's milk was added to the diet. No vitamins were given. Thus, a prolonged state of malnutrition apparently led to chronic thiamine deficiency. The infection of the upper respiratory tract may have served as the trigger mechanism and played the role of a precipitating factor causing the acute, severe thiamine deficiency clinically manifested by Wernicke's syndrome.

In this connection Alexander [6c] (in discussing Zimmerman's paper [6a]) emphasized that Wernicke's syndrome occurs mainly in chronic thiamine deficiency, although he and his associates were able to produce in their animals an acute stage of deficiency manifested by Wernicke's syndrome by increasing acutely the demand for thiamine through adding other vitamins or through a fish diet which contained a thiaminase. In this

12. Spillane, J. D.: Nutritional Disorders of the Nervous System, Baltimore, Williams & Wilkins Company, 1947, chap. 5.

13. Fehily, L.: Infantile Beriberi in Hongkong, Caduceus **19**:78, 1940.

patient there was probably a chronic thiamine deficiency and an acute state of deficiency was brought about by the infection. These facts may explain also the reason cases of Wernicke's syndrome are not seen among infants of the age group in which infantile beriberi is usually encountered (1 to 3 months), since this form probably represents an acute form of thiamine deficiency combined with the results of the toxic action of the milk of the beriberic mother.[18]

SUMMARY

1. Two female Filipino infants, 16 and 10 months of age, respectively, presented typical Wernicke's syndrome and responded quickly to therapy with thiamine and vitamin B complex preparations. The syndrome consists of drowsiness, ophthalmoplegia, severe muscular weakness including head drop, loss of reflexes and pronounced anorexia.

2. The condition is attributed to chronic thiamine deficiency resulting from faulty diet. In one of the infants, an infection of the upper respiratory tract and in the other, an infection of the upper respiratory tract complicating chronic dyspepsia were probably the precipitating factors of Wernicke's syndrome, which was interpreted as a manifestation of an acute thiamine deficiency.

3. The relation of Wernicke's syndrome to infantile beriberi is discussed briefly.

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Progress in Pediatrics

PRESENT TREATMENT OF INFLUENZAL MENINGITIS

Review of Literature and Report on Twenty-Two Patients Treated with Streptomycin and Sulfadiazine

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IN EVALUATING the results obtained from the treatment of Hemophilus influenzae meningitis with streptomycin, we should like to review the literature, as well as report on a series of 22 patients treated by us in the last two years.

While there are several types of influenzal bacilli, beginning with type A up to type F, which affect the meninges in young children, the bacillus H. influenzae is the outstanding causative agent of this disease and is demonstrated in approximately 90 per cent of patients treated.

The bacterial diagnosis of H. influenzae can be made by staining by Gram's method the sedimented spinal fluid, in which the organism found is an extremely pleomorphic gram-negative rod. It may also be filamentous at times. It can be grown easily on fresh chocolate blood agar.

An outstanding feature of the growth of hemophilus bacilli is the satellite phenomenon. When H. influenzae and staphylococci are grown together on the plate, one can see a more luxuriant growth of H. influenzae in the area about the staphylococci. The increased growth is due primarily to the liberation of the V factor by the staphylococci, and the phenomenon can be used as an aid in the presumptive bacteriologic diagnosis of H. influenzae when it is cultured from the spinal fluid.

Serologically, this organism may be identified by the observation of smooth and rough colonies, and the specificity may be demonstrated by the quellung reaction, either directly with the spinal fluid or indirectly with the cultured organisms.

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REVIEW OF THE LITERATURE

The sensitivity of streptomycin on type B H. influenzae was demonstrated by Alexander and her associates,[1] following the studies by Waksman [2] and others on the antibacterial action of streptomycin on a great number of gram-negative organisms. Alexander and her associates demonstrated in vitro the sensitivity of a given strain of organisms to the minimal dose of streptomycin necessary to protect mice against lethal infection with the same strain. They were of the opinion that

> . . . these results seemed to warrant a therapeutic trial with streptomycin even though rabbit antibody along with sulfadiazine has proved so successful in the treatment of influenzal meningitis.

Keefer and the Committee on Chemotherapeutic and Other Agents [3] report the results of a study of 1,000 patients with various infections treated with streptomycin. We are primarily interested in their results from the pooling of 45 different studies made on the use of streptomycin in various diseases, but especially on the use of this drug in type B H. influenzae meningitis. In their report they give a detailed study of streptomycin, its dosage, proper use and toxicity.

According to this report, streptomycin may be used as either the sulfate or the hydrochloride. Both these salts are soluble in distilled water or Ringer's solution. As much as 100 to 175 mg. may be diluted in 1 cc. of fluid for intramuscular injections, and from 50 to 100 mg. may be dissolved in 5 to 10 cc. of solution for intrathecal injections. It is certainly important that the solution should be small in amount so as to produce as little pain as possible.

While these authors suggest many routes of administration of streptomycin in general, intramuscular and intrathecal routes seem to be the choice in the treatment of meningitis. Practically no results have been obtained through oral administration, and this method should be abandoned for the present.

The time elapsing between one injection and the following one has been questioned, since many authors have been of the opinion that a sufficient number of antibodies can be produced even when streptomycin is given at longer intervals, and that the blood serum level can be

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1. Alexander, H. E.; Leidy, G.; Rake, G., and Donovick, R.: Hemophilus Influenzae Meningitis Treated with Streptomycin, J. A. M. A. **132**:434 (Oct. 26) 1946.

2. Waksman, S. A.: Production and Activity of Streptomycin, J. Bact. **46**:299 (April) 1943.

3. Streptomycin in the Treatment of Infections: A Report of One Thousand Cases, The Committee on Chemotherapeutic and Other Agents, National Research Council, J. A. M. A. **132**:4 (Sept. 7) 1946.

kept just as high when the medicament is given in larger doses and less often. However, the maximum serum level of streptomycin can be obtained any time between one and three hours after a single injection and from then on the level decreases. For that reason, we believe that more effective results may be obtained by intramuscular injections every three to four hours and by single intrathecal injections given daily. Since the injection of streptomycin into the blood seems to show that little of the antibody is diffused in the spinal fluid when the intramuscular route is used, it is of utmost importance that intrathecal therapy should be used in conjunction with intramuscular therapy in the treatment of influenzal meningitis.

Keefer and his co-workers express the view that the dose of streptomycin injected intrathecally should be between 25 and 100 mg. dissolved in 5 to 10 cc. of water and given every twenty-four hours because the drug is absorbed slowly from the subarachnoid space. Our dose has been about 32 mg. dissolved in 5 cc. of distilled water. We shall describe this dosage later.

While streptomycin has been used in many diseases by nebulization, this method cannot be recommended as a substitute for intrathecal injections because so little of the streptomycin is diffused from the blood into the cerebrospinal fluid. Most of the drug is excreted by the kidneys into the urine.

Results in the Literature of Treatment of Influenzal Meningitis with Streptomycin.—Before describing the results obtained by Keefer and his associates, we might give a summary of the results obtained by these authors in the use of streptomycin in the treatment of influenzal meningitis. They particularly stressed the fact that infections due to a single organism respond oftener than do mixed infections; that the adequate dosage for blood levels in which streptomycin is effective should be 1 to 2 Gm. per day for five to eight days, and that certainly all patients to whom streptomycin is given should be studied carefully in order to define the nature of the infection, the sensitivity of the organism and the nature of the underlying anatomic lesion.

Their report on the use of streptomycin for 100 patients with H. influenzae meningitis is most interesting. Seventeen of their patients died; 66 were cured clinically and bacteriologically while under treatment; 13 improved under treatment and finally recovered; 1 improved but relapsed, and 3 showed no effect. Of the 66 patients who recovered, 18 received no other treatment than streptomycin, while 48 patients had received previous treatment and 32 were given streptomycin therapy along with penicillin, sulfonamide drugs and serum in different combinations. The average daily dose for all patients who recovered was about 0.5 Gm. intramuscularly and 0.06 Gm.

intrathecally for nine and seven days, respectively. However, in cases in which the treatment failed the dosage was the same but the patients were treated for a shorter time.

In reviewing the 17 deaths, they state that most of the patients were under 3 years of age. A great number of these patients were treated late in the course of the disease and some after other treatment had failed. In 65 per cent of the patients, death occurred five days or less after streptomycin was started and 2 patients received therapy only intramuscularly.

They conclude that the factor most unfavorable for streptomycin therapy is late treatment, especially after other forms of therapy have failed.

It is interesting to note that these authors agree that few untoward reactions occur when moderate dosage is used. The frequency of reaction increased with the increasing dosage. The commonest reactions they observed were eosinophilia, fever, vertigo, paresthesias, histamine-like reactions, flushing of the skin and some neurologic disturbances.

Weinstein [4] states his opinion that streptomycin should be employed in the treatment of H. influenzae meningitis because a great number of deaths are still reported in cases in which type specific antiserum and sulfadiazine are used. He also expresses the view that the use of serum always carries with it the risk of immediate or late reaction, according to the sensitivity of the patient to the serum. He states that the purpose of his work was to determine the effect of streptomycin on the clinical course of influenzal meningitis and to study the rate of the disappearance of the causative organism in the blood stream and spinal fluid, also to note any toxic effects that may result from the use of large amounts of the drug.

He did not use streptomycin in any patient until the diagnosis of meningitis due to H. influenzae was established by bacteriologic methods. Sometimes, by using the quellung test, he was able to detect the causative agent by direct examination of the spinal fluid. In other patients it was impossible to make the diagnosis for two to three days, and in his opinion he was justified in withholding all therapy until the organism was determined. For patients in whom the causative organism was not established, other medication than streptomycin was used.

His dosage administered intramuscularly was anywhere from 120,000 to 1,000,000 units and intrathecally, from 10,000 to 100,000 units. He gave his intramuscular injections at three hour intervals and only one intrathecal injection every twelve to twenty-four hours. The length of treatment continued from seven to nineteen days intramus-

4. Weinstein, L.: The Treatment of Meningitis Due to Hemophilus Influenzae with Streptomycin, New England J. Med. **235**:101 (July 25) 1946.

cularly, and for at least four to seven days longer intrathecally. He was able to determine the level of streptomycin in the serum and spinal fluid.

All patients treated with streptomycin were observed for two weeks after therapy was discontinued and were seen from two to six weeks later to note whether any sequelae developed.

Of the 9 patients treated by Weinstein with streptomycin alone, good results were obtained in 7. Seven of the 9 had the type B organism; the other 2 had neither type A nor type B bacteria.

The age of the patients infected with type B organisms varied from 4 months to 3 years, while the patients from whom the other strains were recovered were 4 months and 5 years of age, respectively.

Of the 2 patients who died, one, 10 months old, was infected with the type B organism, which disappeared from the spinal fluid and blood after twenty-four hours of streptomycin treatment. Staphylococcic bronchopneumonia finally developed in this patient and he died. On autopsy there was little to be seen in the brain and the culture was sterile. The other patient died of persistent influenzal bacterial infection which showed no response to treatment. H. influenzae, type unknown, was cultured from the brain at autopsy.

In this study Weinstein states that his purpose was only to determine the value of streptomycin alone in the treatment of influenzal meningitis. Therefore, in patients to whom other treatment was given prior to his seeing them, at least twenty-four to forty-eight hours were allowed to elapse without therapy before streptomycin was administered. This was done primarily to eliminate the possibility of the use of two agents at the same time. He noted that, even in patients in whom sulfonamide compounds were used previous to streptomycin, organisms were seen in the spinal fluid in spite of the presence of adequate blood concentrations of the sulfonamide drugs. Occasionally, however, some clinical improvement was seen during the period of sulfadiazine therapy and this demonstrated to him that the infection of the meninges had been partially inhibited but not eradicated by the sulfonamide agent.

He chose his dosage and time of administration more or less arbitrarily. Some patients received a small amount of streptomycin and others between 800,000 and 1,000,000 units in divided intramuscular doses every three hours. Besides this, each patient received from 20,000 to 100,000 units of the drug intrathecally. At one time he considered the possibility of using this drug only by the intrathecal route and omitting the intramuscular route, but since 70 per cent of the patients usually have concurrent bacteremia he concluded that it was advisable to use both methods. He expressed his view, however, that the length of time used in intramuscular therapy can be reduced,

since the blood is demonstrated to be sterile after twenty-four to forty-eight hours' treatment.

He is impressed with the fact that the spinal fluid and blood are usually sterile of H. influenzae in twenty-four to forty-eight hours following the use of streptomycin. He is also impressed with the fact that patients who died had a staphylococcic infection in the nasopharynx, and he states the belief that the use of streptomycin allows the relatively insusceptible organisms like staphylococci to increase rapidly in number and virulence. For that reason he suggests the possibility of using penicillin in combination with streptomycin so as to avoid other organisms.

He concludes that, although the number of patients reported on is small, in most cases streptomycin is an effective agent in the treatment of meningitis and bacteremia due to H. influenzae. In his opinion, it is the drug of choice in these diseases.

Brescia and Blaso [5] report the study of 5 patients with H. influenzae type B meningitis treated with streptomycin with 100 per cent recovery. The ages of the patients were respectively 4 months, 9 months, 3 years, 6 years and 9 years. They are of the general opinion that the introduction of streptomycin in the treatment of these patients has given a new point of view as far as prognosis is concerned, while the use of type specific serum, sulfonamide drugs and penicillin gave indifferent and inconsistent results.

In several of their cases streptomycin was complemented with sulfadiazine, but they are of the strong belief that streptomycin was primarily responsible for the cure of these patients. In 1 case they report the use of 250 mg. of streptomycin intrathecally and, following that, 125 mg. intrathecally for three successive days. They had no complications.

Hoyne and his associates [6] report on 3 patients with influenzal meningitis with excellent recoveries.

The first patient was a 3 year old child who was critically ill. To this particular patient streptomycin was not administered until he had been hospitalized three weeks. A total of 50 mg. was given in two equal doses intrathecally forty-eight hours apart and 4,200 mg. given intramuscularly in 140 mg. doses every three hours. Ten days after injection of the anti-influenza serum the patient had severe urticaria. He was critically ill and had pronounced muscular weakness. Thirty-eight days after his discharge from the hospital the patient showed definite improvement, was mentally alert, but still had some incoordination of the left hand and leg.

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5. Brescia, M. A., and Blaso, W. J.: Influenzae Type B Meningitis: Report of Case Cured by Streptomycin, Arch. Pediat. **64**:564 (Nov.) 1947.

6. Hoyne, A. L.; Brown, R. H., and Drucker, A. P.: Influenzal Meningitis Treated with Streptomycin: Report of Three Cases with Recoveries, Arch. Pediat. **63**:559 (Nov.) 1946.

The second patient was a 13 month old white boy with history of stiffness of the neck for seventy-two hours. The patient's spinal fluid showed H. influenzae type B infection. Streptomycin therapy was begun on third day in the hospital. A total of 75 mg. was given in three equal doses intrathecally twenty-four hours apart, and a total of 2,700 mg. given intramuscularly in 90 mg. doses every three hours. This patient was also given anti-influenza serum and showed urticaria. No residuum was noted at the time of release.

The third patient was a 9½ year old white girl who was ill for ninety-six hours. Both the smear and spinal puncture showed the organism of H. influenzae type B and the blood culture was also positive. She received 75 mg. of streptomycin in three equal doses intrathecally during the third day in the hospital and a total of 5,700 mg. intramuscularly in 190 mg. doses every three hours. This patient also had urticaria following anti-influenza (Alexander) serum. She was discharged from the hospital, still showing some difficulty in orientation. Fifty-one days after her discharge the sensorium returned to normal, but she had a persistent slight nystagmus when she looked to the extreme left or right.

Hoyne and his co-workers are of the opinion that influenzal meningitis can be treated successfully with streptomycin; however, they express their belief that good results may be obtained without intrathecal therapy when adequate amounts of streptomycin are administered intramuscularly. This method will be described later in the paper, as another publication by these authors has appeared in the literature recently.

Nussbaum and his associates [7] report a study of 3 patients with influenzal meningitis treated with streptomycin and sulfadiazine. The patients were less than 2 years of age and recovered without any complications or sequelae. Penicillin was given to all these children both intrathecally and intramuscularly until a definite report on the spinal fluid demonstrated, both on culture and smear, H. influenzae type B. They gave the patient with an attack of average severity about 50,000 units intramuscularly every three hours for eight days and doses of 15,000 units the first day and 50,000 the other days intrathecally for three days. They continued the use of sulfadiazine altogether for about thirty days. These authors' opinion at the time was that sulfadiazine should be used in their series because they were not sure of the action of the streptomycin alone, and they expressed the view that some benefit was obtained from the use of sulfadiazine along with the streptomycin.

Logan and Herrell [8] used streptomycin concurrently with some form of sulfonamide drug and antiserum in the treatment of meningitis due to H. influenzae.

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7. Nussbaum, S.; Goodman, S.; Robinson, C., and Ray, L.: Influenzal Meningitis: Report of Three Cases Treated with Streptomycin and Sulfadiazine, J. Pediat. **29**:14 (July) 1946.

8. Logan, G. B., and Herrell, W. E.: Streptomycin in the Treatment of Influenzal Meningitis of Children, Proc. Staff Meet., Mayo Clin. **21**:393 (Oct. 16) 1946.

They treated 4 patients.

The first was a child 5 years of age who was found to have a low sugar level in the cerebrospinal fluid, 9 mg. per hundred cubic centimeters, and stained smear of the fluid showed gram-negative bacilli which proved to be H. influenzae type B by the capsular swelling test. This child was given 2.5 Gm. of sulfadiazine sodium subcutaneously in three divided doses the first day. The following day she received 3.75 Gm. of sulfadiazine sodium intravenously in three divided doses. This patient showed gross hematuria. Use of sulfadiazine was discontinued, and an amount of type specific rabbit antiserum containing 75 mg. of antibody nitrogen was given intravenously. On the third day after her admission, administration of streptomycin was begun. The first dose consisted of 50,000 units given intrathecally; the child also received 50,000 units of streptomycin intramuscularly every three hours. This dosage was increased to 100,000 units every three hours intramuscularly for two days. At the same time, streptomycin was given intrathecally, and a total of 200,000 units was given in that way. After the administration of streptomycin, the patient was given sulfamerazine, about 3 Gm. daily, for two and a half weeks. The child recovered and is in the best of health.

The second child was a white girl 8 months of age. On the sixth day after her admission, she revealed on spinal puncture an increase of cells, with a smear showing gram-negative rods. The culture was positive for H. influenzae type B. In this case, the dosage of streptomycin consisted of 100,000 units given subcutaneously or intramuscularly every three hours. No streptomycin was given intrathecally. Examination of the spinal fluid while the patient was under treatment showed that antibacterial amounts of the drug had diffused into the spinal fluid. Sulfadiazine sodium was given in 5 per cent aqueous solution in the dosage of 10 cc. four times daily. After eleven days, the medicament was given by mouth in the same dosage; this was continued for fourteen days. On the fifth day after her admission, the culture was still positive. Diluted serum was then administered intrathecally (10 mg. of antibody nitrogen) and intravenously (65 mg. of antibody nitrogen). Use of streptomycin was continued for eleven days. The fluid became negative for H. influenzae, and the sugar content never fell below 55 mg. The child made an uneventful recovery.

The third patient was a 16 month old white boy. Diagnosis was made before his admission after an illness of five days. Before his admission the patient received 5,000 to 15,000 units of penicillin intramuscularly and also sulfadiazine by mouth. An attempt was made to inject type specific serum intravenously, but only 6 cc. could be given; so about 16 cc. of it was given intramuscularly. In the hospital he was given sulfadiazine therapy for about two days and then it was discontinued and streptomycin was begun. He received 300,000 units on the first day, 800,000 units daily for nine days and 600,000 units on the last day of administration. It was administered both subcutaneously and intramuscularly. Besides this treatment, he received intrathecal injections of 100,000 units every forty-eight hours for five doses, totaling 8,100,000 units of streptomycin subcutaneously and intramuscularly and 500,000 units intrathecally. The culture became negative forty-eight hours after treatment.

Many more spinal fluid determinations were performed on this patient than is the usual practice, and this was done primarily to follow the possible effectiveness of streptomycin. Even at the time of his dismissal from the hospital the spinal fluid contained about 80 lymphocytes per cubic millimeter. Whether this resulted from the use of streptomycin or from repeated spinal punctures cannot be stated, but the culture remained negative following the use of streptomycin. This patient

was given 35 grains (2.27 Gm.) of sulfadiazine for two weeks following the completion of streptomycin therapy. On the twenty-fourth day in the hospital this particular patient had difficulty in hearing. Six months later his general condition was the same, but he was still unable to hear.

The fourth patient was a 16 month old white boy. At the time of his admission, he had been ill for twenty-three days. In spite of the fact that he was treated intensively with sulfadiazine, the smear showed gram-negative rods and the culture was positive for H. influenzae type B. The sugar content of the spinal fluid was 13 mg.

Streptomycin therapy was begun. This patient received approximately 1,000,000 units intramuscularly every day for the next nineteen days. In addition, he received 100,000 units of streptomycin intrathecally. Forty-eight hours after streptomycin therapy was begun, the culture of the spinal fluid became negative.

These authors made special studies of the cerebrospinal fluid to determine the amount of streptomycin present when the patient was receiving streptomycin by the intramuscular route only. Since there were apparently adequate amounts of streptomycin in the fluid, intrathecal therapy was not continued. There was usually from 15 to 30 units present in the spinal fluid.

In spite of the fact that this patient apparently was doing well, from laboratory observations, he did not seem to be improving clinically. Six days after the beginning of streptomycin therapy, he was given 45 grains (2.9 Gm.) of sulfadiazine daily for five days and serum therapy was administered, with the patient receiving four injections of the immune serum. It was evident when sulfadiazine and serum therapy was begun that this patient had a hydrocephalic appearance. This patient never became conscious, and on the twenty-eighth day following his admission a Torkildsen operation was performed because of the postmeningitic hydrocephalus. The patient lived until the sixtieth day after his admission to the hospital. Autopsy showed hydrocephalus with increased intracranial pressure.

In this case the authors are of the opinion that, although streptomycin therapy resulted in eradication of the organism, it did not prevent the accumulation of purulent material at the base of the brain and over its surface which so commonly occurs in patients whose meninges are infected with H. influenzae type B. Death resulted not from the infection, but from the hydrocephalus.

All these patients received, at one time or another, sulfonamide therapy, but only after the use of streptomycin did the culture of the spinal fluid become negative. There was other laboratory evidence of improvement which occurred only after the use of streptomycin had begun.

In the report referred to previously in this paper, Alexander and her associates,[1] following the demonstration by Waksman [2] of the antibacterial action of streptomycin on a number of gram-negative organisms, suggested that type B H. influenzae might be sensitive to this antibiotic substance. In vitro they demonstrated that one dose of a suitable quantity of streptomycin was superior to type specific antibody used in conjunction with sulfadiazine in protecting mice against lethal infections caused by type B H. influenzae.

In a series in which streptomycin was used alone, the patients received approximately 20,000 units of streptomycin per pound (0.5 Kg.) of body weight in each twenty-four hour period. Administration was either by the continuous intramuscular drip method, with the antibiotic substance diluted in 240 cc. of isotonic solution of sodium chloride, or by interrupted intramuscular injections every three hours in a concentration of 50,000 units or less per cubic centimeter. This drug was also administered intrathecally to all patients, the injection being given once a day and the dose being between 25,000 and 50,000 units, depending on the severity of the infection.

The authors studied carefully the concentration of streptomycin in the serum and the spinal fluid of the patients. This is a difficult procedure to perform in the average hospital, and yet these authors express the view that streptomycin should not be administered unless the serum and spinal fluid levels can be watched carefully.

As to the toxicity of streptomycin, Alexander and her co-workers observed commonly an increase of albumin, red cells and epithelial cells in the urine. This increase did not persist after the withdrawal of the drug, and there seemed to be no evidence of permanent damage to the kidney. They also report that this may have been the result of impurities of the preparation rather than of the streptomycin itself. Another manifestation which in their opinion was due to concomitant impurities was a comatose condition observed in 2 infants after the second intrathecal injection of 50,000 units of streptomycin. Improvement was seen within twelve hours after temporary withdrawal of streptomycin. One of these patients made an uneventful recovery, and the other one, who died several days after the spinal fluid cultures became sterile, showed a subarachnoid abscess. Later preparations of streptomycin in the same quantity failed to elicit these reactions. One of their patients showed damage to the eighth cranial nerve which resulted in deafness.

Results of Treatment with Streptomycin in General.—Alexander and her associates report that of the 25 patients treated 12 had mild or moderately severe infections and recovered after treatment with streptomycin alone. All these patients received sulfadiazine with or without penicillin prior to their admission and were ill on an average of eight days or less. The severity of disease was judged by clinical manifestations and the concentration of sugar in the spinal fluid. Four of the 5 patients with severe infections had had meningitis for two weeks or more. Alexander and her co-workers are of the opinion that prognosis for recovery of these patients would have been poor under any known treatment. One of these patients was in a semicomatose state when he arrived at the hospital, and the sugar level of the spinal

fluid was only 6 mg. per hundred cubic centimeters. All 5 patients received streptomycin therapy alone initially, but in 3 of them unsatisfactory response led to the administration of type specific antiserum after four days of streptomycin treatment. In 1 child the organisms were completely resistant to streptomycin, and, after the addition of antiserum and sulfadiazine, recovery was prompt and complete. Two other patients who received antiserum and sulfadiazine after four days of streptomycin therapy disclosed evidence of serious cerebral damage. Two patients who were treated with streptomycin alone without additional therapy died of the infection. Four patients received streptomycin after unsuccessful therapy with antiserum and sulfadiazine. Three of these children received sufficient therapy with these agents, while 1 received less than an adequate amount. In 1 of these patients streptomycin was responsible for the prompt elimination of the infection.

In general, it can be said that, although clinical improvement was less rapid than that seen after antiserum therapy, the changes in the spinal fluid which indicate a clearance of infection appeared just as promptly. This can be better demonstrated by a series of 9 of 12 patients in whom the spinal fluid was sterile twenty-four hours after initiation of streptomycin therapy, and in the other 3 after forty-eight hours. The return to normal of the chemical constituents of the spinal fluid was equally rapid.

One particular patient, a 2 year old child, gave Alexander and her co-workers an opportunity to test the use of this antibiotic substance alone in the course of a severe infection. This patient was extremely ill; within twelve hours after streptomycin therapy was begun, the smear of the spinal fluid showed a decisive change, and it was difficult to find convincing organisms. The patient's spinal fluid chemistry improved, and one intrathecal dose of streptomycin was considered adequate, although the temperature was still 104 F. and there was apparently no further clinical improvement. By the morning of the fourth day it was obvious that the intrathecal introduction of streptomycin should be resumed. The culture of the spinal fluid made twenty-four hours after the initiation of streptomycin therapy, as well as the cultures twelve to twenty-four hours later, revealed the growth of H. influenzae. Twenty-five thousand units of streptomycin was introduced intrathecally in each twelve hour period, and after thirty-six hours the patient became worse. The sensitivity tests showed that the organisms were streptomycin resistant. Streptomycin therapy was then discontinued, and the patient was given rabbit antiserum and sulfadiazine. Forty-eight hours after treatment, the spinal fluid became sterile and the temperature was lower. The course of this patient's illness was stormy, as he had signs of hemiparesis. Four weeks later he showed some improvement, and, in the authors' opinion, there was rather extensive injury to the left motor area four days after initiation of streptomycin. However, they have had several cases similar to this one in which the involvement of the motor area showed improvement and recovery in less than a month.

In general, these authors are of the view that when meningitis is mild or moderately severe streptomycin alone will prove a sufficient

agent; however when, as shown by laboratory and clinical examination, the disease is severe, the outcome of the use of streptomycin alone is poor indeed, especially when the results of neurologic examination indicate injury to cerebral cells.

Their opinion at present is that the use of this drug should be limited to those institutions which are equipped not only to follow the patient by ordinary bacteriologic and chemical procedures but also to test the sensitivity of any strain isolated in the patient's spinal fluid. They suggest when severe meningitis is present that all three agents, that is, rabbit antiserum, sulfadiazine and streptomycin, be used.

These authors report 3 deaths. One was in a patient 2 months of age; the duration of disease was twenty-one days; both sulfadiazine and penicillin were used prior to his admission. No antiserum was given in the hospital. The next was in a child 1 year 1 month of age who received sulfadiazine and penicillin one day before his admission and no rabbit antiserum. The last was in a patient 1 year of age in whom streptomycin was used after failure of antiserum and sulfadiazine. The patient received antiserum for ten days and sulfadiazine for two days. The authors state their belief, in general, that it is the severity of infection and, therefore, the size of the bacterial population which determine whether the strain of a given patient will become resistant, because when the population is large enough a certain number of organisms will be resistant to any antibacterial agent.

Butler and his associates [9] stated their opinion that, as it has been stressed generally, early diagnosis and prompt institution of adequate therapy are of the utmost importance in the outcome of influenzal meningitis. They report on 1 patient 3 months of age for whom a positive diagnosis of H. influenzae type B was made. The patient was given sulfadiazine and then started on streptomycin, 25,000 units intrathecally once daily and 30,000 units intramuscularly every three hours. By the third day in the hospital the patient seemed better. Antiserum, (50 mg. of antibody nitrogen) was given on the fourth day in the hospital, but the patient continued to have a positive quellung reaction and the fluid had many pleomorphic forms of H. influenzae. Use of streptomycin was continued, and the baby slowly improved and was discharged on the sixteenth day after the first appearance of organisms in the spinal fluid.

Birmingham and his associates [10] report on a series of 8 patients with H. influenzae type B who were treated with streptomycin either

9. Butler, L. J.; Yow, M. D., and Reinhart, J. B.: Meningitis Due to Hemophilus Influenzae: Report of Case Treated with Sulfadiazine, Streptomycin, and Antiserum, with Recovery, North Carolina M. J. **7**:8 (Jan.) 1946.

10. Birmingham, J. R.; Kaye, R., and Smith, M. H. D.: Streptomycin in the Treatment of Influenzal Meningitis, J. Pediat. **29**:1 (July) 1946.

from the beginning of therapy or after unsuccessful treatment with other therapeutic agents. They gave an average of 20,000 to 25,000 units of streptomycin intrathecally and of 10,000 to 50,000 units intramuscularly. They state the belief that in the 4 patients who recovered during treatment with streptomycin the drug played the predominant role in eradicating the infection. While 1 of the patients received rabbit antiserum, they still are of the opinion that the fluid became permanently sterile on the day after they started the streptomycin therapy and that the growth of the organisms was stopped by the streptomycin.

They report 3 deaths in this series. One of the deaths in their opinion was due to overwhelming infection. That of the second patient they view as due to a decided decrease in the sensitivity of the organisms to streptomycin, and they are of the opinion that larger doses of streptomycin should have been given initially in order to avoid drug resistance. The third patient, they state, surely received streptomycin in inadequate doses. Primarily, in their opinion the cause of death in their patients was not initiating larger doses of streptomycin in the early days of the disease.

Hoyne and Brown [11] are strongly in favor of the use of the lumbar puncture for diagnostic purposes alone. Hoyne, in particular, expresses his view that most persons who use the intrathecal procedure do so because it has been an old established method to treat meningitis in this manner. Twelve years ago, he reported the use of serum intravenously in meningococcic meningitis, showing its advantages, especially in lowering the fatality rates when large doses were used and when intrathecal therapy was abandoned. This method was later applied to all forms of meningitis, and he [12] is convinced that one spinal tap for diagnosis is sufficient for any type of meningitis.

He cites the work of Smith and her associates [13] who reported on 28 patients with influenzal meningitis of whom only 2 died. Twenty-five of the 27 patients were treated with antiserum, almost all of it given intravenously, and in 1 patient whose spinal fluid culture remained positive there was apparently no beneficial effect from the intrathecal use of antiserum.

These authors,[13] however, are of the opinion that the spinal fluid tap should be done daily until the spinal fluid sugar level has returned

11. Hoyne, A. L., and Brown, R. H.: Intrathecal Therapy Not Required for H. Influenzae Meningitis: A Report of Twenty-Eight Cases, J. A. M. A. **136**:597 (Feb. 28) 1948.

12. Hoyne, A. L.: Epidemic Meningitis, J. A. M. A. **115**:1852 (Nov. 30) 1940.

13. Smith, M. H. D.; Wilson, P. E., and Hodes, H. L.: Influenzal Meningitis, J. A. M. A. **130**:331 (Feb. 9) 1946.

to normal, but it is Hoyne's view that, while such procedures are of scientific interest, they do not necessarily bring about recovery. He especially comments on the fact that Smith and her co-workers were surprised themselves at the results of their treatment without intrathecal therapy. He quotes them as saying, "owing either to chance or to the use of large doses of serum [the patients] seem to recover without intrathecal serum."

Hoyne reports that Josephi and her associates [14] and Birmingham and his co-workers [10] reported shock and anaphylactic reactions, hydrocephalus and other complications when serum was given intrathecally in meningococcic meningitis. Edmonds and Neter [15] also report that, although specific type B anti-influenza rabbit serum is injected intraspinally for several days, on many occasions the cultures are still positive for H. influenzae.

Edmonds and Neter cite 4 patients to whom serum was given intraspinally and intracisternally and express their opinion that fatalities were due to the fact that many organisms were present in the cerebrospinal fluid at that time.

Hoyne states that, in Chicago, he and his colleagues have treated several thousand patients with meningitis caused by a variety of organisms with remarkable results without resorting to the use of intrathecal therapy. Included among them was the reported series [16] of 16 recoveries from influenzal meningitis in which only 3 patients received intrathecal therapy and the others recovered without it. He expresses his belief that Alexander and her associates [17] conceded that the time required to sterilize the spinal fluid is comparable whether the serum is given intravenously or intrathecally, and yet they seem to display a lack of confidence in the exclusive intravenous therapy.

With the release of streptomycin, Nussbaum and his associates [7] agreed with the National Research Council that streptomycin should be used intrathecally because when used otherwise adequate amounts of this drug do not enter the spinal fluid.

In this present study, Hoyne [11] reports on 28 patients with influenzal meningitis who were treated in the following manner: Eighteen of the

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14. Josephi, M.; Mehlman, M. D., and Hagar, D.: Influenzal Meningitis in a Seven Month Old Infant, J. Pediat. **19**:823 (Dec.) 1941.

15. Edmonds, A. M., and Neter, E.: Appraisal of Treatment of Hemophilus Influenzae Type B Meningitis with Specific Rabbit Serum and Sulfonamides, J. Pediat. **28**:462 (April) 1946.

16. Hoyne, A. L.: Advances in Treatment of Meningitis, J. Pediat. **19**:778 (Dec.) 1941.

17. Alexander, H. E.; Ellis, C., and Leidy, G.: Treatment of Type-Specific Hemophilus Influenzae Infections in Infancy and Childhood, J. Pediat. **20**:673 (June) 1942.

28 patients were treated with streptomycin; 12 patients received streptomycin but no serum. Eleven patients were given streptomycin intramuscularly but had no intrathecal therapy, and 10 of these had no serum therapy. Seven of the patients were given streptomycin intrathecally, as well as intramuscularly, and among these occurred 2 deaths. Five patients received serum but no streptomycin. Six patients were treated with serum, streptomycin and sulfonamide compounds. Five patients were treated with sulfonamide drugs alone. Most of these patients had only one lumbar puncture, and the average number of lumbar punctures for the recovered patients was 2. In all 28 patients the organism was shown to be type B H. influenzae. Every patient coming into the hospital received sulfonamide compound.

The following were the complications in these patients: hydrocephalus, 1; deafness, 1; left hemiplegia, 1; paralysis of the left facial nerve, 1; paresis of the left arm, 2, and serum sickness, 4.

In general, 21 of the 26 patients who recovered received no intrathecal therapy. Hoyne and his associates express the belief that recovery is more prompt and complications are fewer when the intrathecal method is omitted. They consider that the primary purpose of the lumbar puncture is to establish diagnosis, and they state their strong belief that intrathecal therapy is contraindicated for type B H. influenzae meningitis.

REPORT OF CASES

We wish at this time to report the results in the treatment of 22 patients with influenzal meningitis, each of whom had definite hemophilus bacillus type, except 1 for whom the type was undetermined.

We did not feel justified in using streptomycin alone, since it was simple enough to add sulfadiazine for all patients treated. Sulfadiazine alone can apparently cure 30 per cent of the patients treated, but with the addition of streptomycin it seemed possible that better results could be obtained, as will be described later.

The problems of treatment in influenzal meningitis are primarily as follows:

1. The length of the disease previous to treatment.

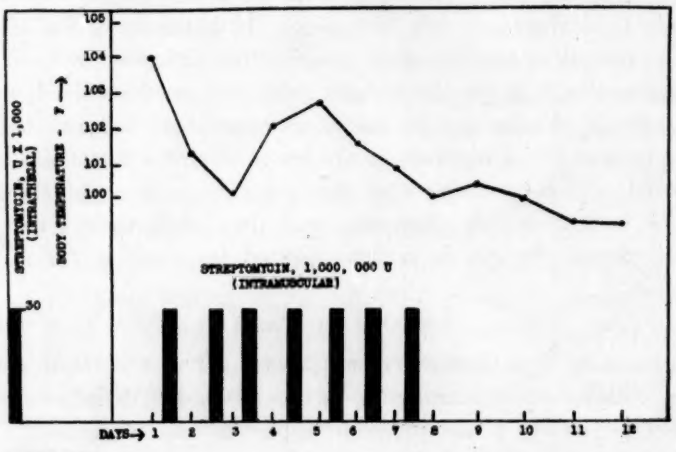
2. The age of the patient. Certainly patients below 6 months of age are to be considered as less amenable to treatment than older patients.

3. The level of sugar in the spinal fluid, which is of the greatest importance. We believe, as Alexander and her associates state, that patients showing less than 15 mg. of sugar per hundred cubic centimeters of spinal fluid should be considered as seriously ill.

4. The number of streptomycin-fast organisms in the spinal fluid, a factor which plays a great part in retarding the treatment of this

form of meningitis. This means the longer the disease lasts the more opportunity streptomycin-fast organisms have to develop and to be the cause of fatalities. Thus, patients on whom treatment is begun early in the disease have a greater opportunity to get well.

Method of Treatment.—All our patients received sulfadiazine, usually in the form of sulfadiazine sodium, 1½ grains (0.09 Gm.) per pound of body weight subcutaneously or in drip form, until the patient was able to take this type of medication by mouth. The length of treatment usually was prolonged about ten days after the discontinuance of the use of streptomycin. The drug was given for this period regardless of previous therapy before the patient's admission to the hospital.



SPINAL FLUID								
CELLS, X 100	20	80.5	9.8	0.8	0.8	-	0.5	0.3
SUGAR, MG.%	35	37	66	-	75	-	-	58
PROTEIN, MG.%	142	40	-	-	76	-	-	54
CULTURE	+	0	0	0	0	0	0	0

Chart illustrating the complete course of an average case of influenzal meningitis treated with streptomycin and sulfadiazine.

Most of the patients received 5,000 units of penicillin intrathecally until a positive culture could be obtained for H. influenzae. Streptomycin was not used for any patients except those in whom definite proof of the disease was obtained.

Streptomycin was given intramuscularly in the dosage of 1 Gm. per day, regardless of the weight of the patient. This was done primarily because we felt that the drug would be used for only a short period; that toxic symptoms would probably not develop during this period following the use of streptomycin, and that, if possible, all bacteria would be cleared in ample time so as to remove the possibility

of the increased growth of streptomycin-resistant bacteria in the colonies of influenzal bacilli.

The drug was dissolved in about 8 cc. of water, and 1 cc. of the solution was given every three hours intramuscularly for four to seven days, according to the seriousness of the illness of the patient. At the same time approximately 32 mg. of streptomycin was given intrathecally for the same number of days.

TABLE 1.—*Data on First Series of Patients*

Age	Duration of Disease, Days	Previous Therapy, Duration	First Spinal Fluid Sugar Level, Mg./100 Cc.	Spinal Fluid Sterile, Days	Streptomycin: Intramuscularly, Days	Streptomycin: Intrathecally, Thousands of Units	Result
3 mo.	6	Sulfadiazine, 3 days; penicillin, 1 injection	46	1st, positive; 2d, negative	7	30 × 7 days	Recovered
5 mo.	7	Sulfadiazine, 7 days; penicillin, 1 day	80	1st, negative; 2d, positive; 3d, negative	7	30 × 7 days	Recovered
5 wk.	1	Sulfadiazine, 1 day; penicillin, 1 tablet	86	1st, negative; 2d, positive; quellung with type B H. influenzae	7	30 × 7 days	Recovered
6 mo.	4	Sulfadiazine, 4 days; penicillin, 4 days	22	1st, positive; 2d, negative	7	30 × 7 days	Recovered
6 mo.	1	None	20	1st, positive; 2d, negative	7	30 × 7 days	Recovered
4 mo.	2	Sulfadiazine; penicillin	42	1st, positive; 2d, negative	8	30 × 4 days	Recovered
2 mo.	6	None	16	Positive			Died 13 hours after admission
5 mo.	16	Sulfadiazine; penicillin	17	1st, positive; 2d, negative	10	80 × 10 days; 100 mg. antiserum (Alexander)	Died 11 days after admission: abscess at cerebellum; thick exudate of meninges; especially at base of brain
1 day	1	None	Not reported	1st, positive: H. influenzae, type undetermined; 2d day negative	8	30 × 2 days	Recovered

Anti-influenza (Alexander's) rabbit serum was not used except in 2 cases. This will be discussed later.

Results of Treatment.—The first group of patients numbered 9. The ages follow: 1, 1 day; 1, 5 weeks; 1, 2 months; 1, 3 months; 1, 4 months; 2, 2 months, and 2, 6 months of age.

As may be seen in table 1, the shortest duration of the disease before the patient's admission to the hospital, as far as it could be obtained from the history, was one day, 3 patients being admitted with this record. The longest was sixteen days. The majority of these patients received sulfadiazine and penicillin for some time before their admissions. The lowest sugar level in the spinal fluid was 16 mg. per hundred

cubic centimeters, and the highest was 46 mg. Almost all patients had spinal fluid positive for the organism on the first culture and negative on the second, except 1 patient 5 months of age, culture of whose fluid was negative on the first day and became positive on the second day and negative on third day. Two patients in this series died and their cases will be described later.

The second series consisted of 7 patients, the youngest being 7 months and the oldest 23 months of age. Two patients were 10 months of age; 1, 7 months; 1, 13 months; 1, 15 months; 1, 17 months, and 1, 23 months of age.

TABLE 2.—*Data on Second Series of Patients*

Age, Mo.	Duration of Disease, Days	Previous Therapy, Duration	First Spinal Fluid Sugar Level, Mg./100 Cc.	Spinal Fluid Sterile, Days	Streptomycin: Intramuscularly, Days	Streptomycin: Intrathecally, Thousands of Units	Result
10	21; otitis media; stiffness of neck, 1 day	Sulfadiazine, 1 day; penicillin, 1 day	35	1st, positive; 3d, negative	7	30 × 7 days	Recovered
10	8 hr.; otitis media, 3 wk.	None	35	1st, positive; 3d, negative	7	30 × 7 days	Recovered
7	10	Sulfadiazine	18	1st, positive; 2d, negative	11	30 × 7 days	Recovered
13	3	None	45	1st, positive; 2d, negative	5	30 × 3 days	Recovered
17	2	None	33	1st, positive; 2d, negative	7	30 × 7 days	Recovered
23	4	None	38	1st, positive; 2d, negative	8	30 × 6 days	Recovered
15	3 wk. Pneumonia: recovery; 10 days later became ill again	Sulfadiazine (both illnesses)	20	Culture negative; quellung positive; spinal block	7	30 × 7 days; 100 mg. antiserum (Alexander)	Died 9 days after admission; sinus thrombosis

Two patients came in with a history of duration of the disease for approximately three weeks. One had otitis media and the other had had pneumonia, was well for ten days, then became ill again, and was treated with sulfadiazine until admitted to the hospital.

Four of these patients received no treatment whatsoever, and the duration of the disease was from eight hours to ten days. Two patients 10 months of age had a culture remaining positive for two days, while cultures for the others became negative on the second day. The culture of the 15 month old patient remained negative but the quellung reaction was positive. This patient died and will be reported on with the others who died.

The lowest sugar level in the spinal fluid was 20 mg. and the highest was 45 mg. per hundred cubic centimeters. All patients recovered except the 15 month old child.

The third series consisted of 6 patients from 2 to 7 years of age. Three patients were 2 years; 2, 3 years, and 1, 7 years of age. The duration of disease in this group was from two to eight days. All the patients in this group recovered.

The following are detailed reports on patients who died.

CASE 1.—The patient was 5 months of age, was ill approximately sixteen days before admission and had received, previous to admission, sulfadiazine and penicillin. The spinal fluid showed a culture positive for type B hemophilus bacilli, with 17 mg. of sugar and a white blood cell count of 3,750. The culture became negative after the initial tap. Both cisternal and ventricular punctures were done on this patient, and he had a definite lumbar block. Anti-influenza (Alexander) serum (100 mg. of antibody nitrogen) was given. The temperature persisted between 101 and 106 F. in spite of the use of sulfadiazine and streptomycin intracisternally and by the lumbar route. Autopsy revealed thick purulent exudate of meninges, especially at the base of the brain, with a small abscess at the cerebellum.

TABLE 3.—*Data on Third Series of Patients*

Age	Duration of Disease, Days	Previous Therapy, Duration	First Spinal Fluid Sugar Level, Mg./100 Cc.	Spinal Fluid Sterile, Days	Streptomycin: Intramuscularly, Days	Streptomycin: Intrathecally, Thousands of Units	Result
2 yr.	2	None	33	1st, positive; 2d, negative	7	30 × 7 days	Recovered
2 yr.	2	None	40	1st, positive; 2d, negative	7	30 × 7 days	Recovered
7 yr.	2	None	52	1st, negative; 2d, positive; 3d, negative; smear positive, 4 days	7	30 × 7 days	Recovered
3 yr., 2 wk.	6	Sulfadiazine, 3 days	35	1st, positive; 2d, negative	6	30 × 4 days	Recovered
3½ yr.	8	Sulfadiazine	31	1st, positive; 2d, negative	9	30 × 6 days	Recovered
2 yr.	7	None	23	1st, positive; 2d, negative	7	30 × 7 days	Recovered

CASE 2.—The patient was 2 months of age. His history revealed illness for about six days before his admission with no known therapy given. A spinal puncture on his admission showed a count of 3,600 cells, with 45 mg. of sugar and a culture which was positive for hemophilus bacilli. This patient apparently had a fulminating case of meningitis and died thirteen hours after admission. Streptomycin was given intrathecally and intramuscularly during the stay in the hospital. Permission for autopsy was not obtained.

CASE 3.—The patient was 15 months of age. He became ill about three weeks before his admission, and the local physician diagnosed the illness as pneumonia. He was treated with sulfadiazine and apparently became well. Ten days after the beginning of his illness he became ill again with fever and showed extreme irritability. He was seen about four days after he became ill again. At this time he was extremely lethargic and more comfortable when the head was kept flexed on chest. He could not recognize the members of the family, and they were advised to send him to the hospital.

The patient was admitted with a temperature of 101 F., pulse rate of 160 and respiratory rate of 55. He was greatly dehydrated; the upper extremities were

flexed with the hands clinched; the lower were extended with the limbs rigid, and he presented an internal strabismus of the right eye. The impression at that time was that the condition was influenzal meningitis.

On his admission the child received lumbar and cisternal taps, as described previously, and the H. influenzae organism was identified. Immediate intravenous clysis (2.5 per cent glucose solution in isotonic sodium chloride solution) was begun. In the clysis the child was given an amount containing 100 mg. of antibody nitrogen of H. influenzae type B rabbit serum (Alexander). Twelve hours later the patient's serum quelled the organisms. He was given streptomycin, 1 Gm. intramuscularly daily, with daily lumbar and cisternal taps and instillation of 31 mg. of streptomycin in each site. On two occasions ventricular punctures were done. Because of demonstration of ventricular block streptomycin was introduced in the upper, as well as lower, puncture sites. He was given sulfadiazine sodium, 1 Gm. subcutaneously every twelve hours. In the beginning oral tube feeding was attempted. This becoming unsatisfactory, the child had to be fed parenterally throughout the remainder of his course in the hospital. Two blood transfusions, 150 and 200 cc. of whole blood, were administered on the second and third days after his admission without reaction. The child responded poorly and remained lethargic and comatose. For the first day the temperature ranged between 101 and 103 F., but on the third day it became normal and stayed in that range until the day of death, when a sudden spike carried it to 104 F. On the day before death, tarry bowel movements were observed on the diaper. On the night prior to day of death he vomited repeatedly coffee-ground material. On the morning of the day of death he was seen to become even more spastic, with occasional convulsive movements of head and eyes. Cheyne-Stokes respiration was observed by an attendant on the day of death. The patient died nine days after his admission, and autopsy revealed sagittal sinus thrombosis.

COMMENT

We have presented a review of the literature on the use of streptomycin in influenzal meningitis, and a summary of the cases of 22 patients treated by us with streptomycin, both intramuscularly and intrathecally, in conjunction with sulfadiazine. It is apparent that streptomycin is a valuable drug in the treatment of this once fatal disease. The dosage of this medicament has, as yet, not been established, but we feel that large doses used for a short while are more beneficial than smaller doses, as no toxic symptoms present themselves.

We believe that this is the better method, because the purpose of treatment in such a severe disease should be primarily to eradicate as much as possible the streptomycin-resistant colonies, to kill off the streptomycin-susceptible bacteria and to curtail the new growth of both streptomycin-resistant and streptomycin-susceptible bacteria.

The use of streptomycin intrathecally has been described, and we cannot, as yet, judge whether Hoyne and his associates are justified in using this drug intramuscularly alone. We believe, however, that the use of Alexander's antiserum will not be necessary in the majority of cases because sulfadiazine and streptomycin in themselves are efficacious

in eradicating this condition. With the use of antibiotic substances, the necessity for serums in pneumonia and other diseases has been eliminated, and certainly no better results can be obtained than we have obtained with this series of patients.

The question always arises whether it is of value to save the patient on many occasions and leave him in a vegetative state. This we doubt.

We have had few toxic sequelae in this series of patients. Only 1 case of deafness, which did not persist, and several cases of albuminuria presented themselves.

SUMMARY

A study of 22 patients, with 19 living and well and 3 deaths, with Hemophilus influenzae meningitis present in all except 1, in whom the type of organism could not be determined, is presented.

Our treatment consisted of the use of sulfadiazine in the form of its sodium salt, 1½ grains (0.09 Gm.) per pound (0.5 Kg.) of body weight for ten to fourteen days after the discontinuance of the use of streptomycin. This was given subcutaneously when the patient could not retain it by the oral route.

Streptomycin was given in the dosage of 1 Gm. daily, divided into eight equal doses intramuscularly, and 30 to 32 mg. intrathecally for four to seven days, according to the general condition of the patient and the spinal fluid picture.

Toxic symptoms were negligible in this series of patients, even in those for whom large doses of streptomycin were used. We believe this is due to the fact that young infants tolerate antibiotic substances better than adults.

Anti-influenza rabbit serum (Alexander) was used in only 2 patients who died.

Suite 311, Doctors Building.

News and Comment

GENERAL NEWS

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examinations held at Baltimore on May 7, 8 and 9, 1949:

Gunnard John Antell, Coral Gables, Fla.; Robert Thomas Bandi, Wheeling, W. Va.; George H. Barmeyer, Missoula, Mont.; Leo M. Bashinsky, Birmingham, Ala.; Selma Buchbinder, Rockville Center, N. Y.; Edgar L. Clayton, Levittown, Hicksville, N. Y.; John Fielding Crigler Jr., Baltimore; George F. Cunningham, Brooklyn; Edward Davens, Baltimore; Matthew Debuskey, Baltimore; John Henry Dent, New Orleans; Joseph Dolgin, St. George, Staten Island, N. Y.; Richard Edward Dormont, New Orleans; S. Chester Dunn, Kingsville, Texas; Anny Elston, New York; Theodore S. Golden, Framingham, Mass.; Seymour Gruber, Brooklyn; Harriet Griggs Guild, Baltimore; Janet Baillie Hardy, Baltimore; Paul Harold Hardy Jr., Baltimore; Horace L. Hodes, Baltimore; Laslo Kajdi, Baltimore; Maurice J. Keller, Salem, Mass.; Marjorie B. Klugherz, Brooklyn; Bernard Laski, Toronto, Canada; Harold I. Lecks, Philadelphia; Elizabeth Sarah Linson, Hagerstown, Md.; James Neill Lysaught, Baltimore; Lillian Francis McMackin, Milton, Mass.; Milton Markowitz, Baltimore; Jack Metcoff, Boston; Thomas Edward Mosher, New York; John Oliver Nestor, Arlington, Va.; Thomas Lewis Rider, Albany, N. Y.; Martin Rothman, Haverhill, Mass.; Justin Rubin, Philadelphia; Marie Esther Russell, Collingswood, N. J.; Edward A. Sawan, Akron, Ohio; Alexander J. Schaffer, Baltimore; Francis F. Schwentker, Baltimore; Francis F. Silver, Cleveland; George Roland Spence, Silver Spring, Md.; Melchijah Spragins, Towson, Baltimore; Frank Ashbrook Stewart, Newport, R. I.; James B. Stewart, East Cleveland, Ohio; Ethon L. Stone, Jackson, Mich.; Helen B. Taussig, Baltimore; Grant Taylor, Durham, N. C.; William Joseph Temple, Covington, Ky.; Elizabeth Peabody Trevett, Annapolis, Md., and Maya Stromberg Unna, Lagrange, Ill.

Abstracts from Current Literature

Vitamins; Avitaminoses

SCURVY IN INFANTS. M. BERNHEIM and J. MARTIN, Arch. franç. de pédiat. **3**:539, 1946.

On casual observation it appears that scurvy is uncommon among young subjects, notwithstanding the almost universal use in France of dried milk unfortified with vitamin C and the absence of palatable fruit juices, particularly in the winter months.

As a matter of fact, the author declares, scurvy is common but not always readily apparent; the onset of disease or the development of nutritional problems brings the clinical picture to view. Illustrative case reports confirm this contention.

AMESSE, Denver.

RECENT RESULTS OF VITAMIN RESEARCH. EMIL ABDERHALDEN, Bull. schweiz. Akad. d. med. **2**:331 (May) 1947.

The discovery of an enzyme called thiaminase, which splits thiamine into pyrimidine and thiazole, permits the production of a true vitamin B_1 avitaminosis. This enzyme was demonstrated in species of fish, such as carplike freshwater fish, mackerel and atlantic trout. Vitamin B_6 (pyridoxine) in the form of its derivative, pyridoxal, obtained by esterification with phosphoric acid, is a co-enzyme of a carboxylase which yields the corresponding amine from amino acids by the cleavage of carbonic acid. A deficient intake or absorption of pyridoxine leads to the occurrence of xanthurenic (dioxychinolin carbonic) acid in the urine of certain animals. This acid is derived from tryptophane. Thus, pyridoxine is indispensable for the normal metabolism of amino acids. The folic acid group has been isolated in crystalline form from several different sources, e.g., liver. Its composition was easily elucidated and its synthesis successful. The following vitamins proved to belong to the folic acid group or to be identical with folic acid: Lactobacillus casei factor, vitamin B_c, vitamin M and an antianemia factor in chicks. The following substances are constituents of the vitamins belonging to the folic acid group: 6-oxy-2-aminopteridine, para-aminobenzoic acid and glutamic acid. The components of this vitamin group are derived from various sources and differ by the number of glutamic acid molecules they contain. These molecules are combined with one another in the form of acid amides. It is important to know that the effective principle as such is not always present but must first be liberated from certain substances by the action of enzymes. These are the conjugates and conjugase, the latter being a corboxypolypeptidase which splits off the molecules of glutamic acid. There are types of cells with and types without conjugase. The conjugates have influence on the former cells but not on the latter.

Folic acid influences the growth of certain micro-organisms and is of special importance for its influence on blood formation. In folic acid deficiency macrocytic hyperchromic anemia, granulocytopenia and thrombopenia occur. A favorable influence on sprue and on leukopenia caused by roentgen rays has been proved. The treatment of pernicious anemia is also successful if pure folic acid—also called pteroylglutamic acid—is used. In this disease no conjugase is present; that is the reason the bound folic acid has no effect. Vitamin P is now considered to be an antioxidizing agent. All compounds containing vitamin P protect epinephrine from oxidation. It is assumed that the stability of capillary walls is due to the action

of this vitamin. Vitamin E is also an antioxidizing agent. Its deficiency does not lead to sterility in the male mouse. A new vitamin, called T, promotes the assimilation of foodstuffs and increases vitality. In certain organisms gigantism is induced, even in those which never exhibit overgrowth under normal conditions.

FROM THE AUTHOR'S SUMMARY.

VITAMIN D_2 INTOXICATION. R. DEBRÉ, S. THIEFFRY, E. BRISSAUD and L. TRELLU, Presse méd. **54**:770 (Nov. 16), 1946.

Vitamin D_2 is of tremendous value in the treatment of rickets and tetany, but when given in massive doses it may produce intoxication. The authors describe the symptoms and signs arising in 9 patients who were treated overzealously. Loss of appetite, nausea, polydipsia, polyuria, constipation, loss of weight, pallor and changes in character were the most frequent signs. Hypertension may suggest renal damage; the nonprotein nitrogen of the blood is increased, although the urine usually is completely normal. Hyperglycemia and hypercalcemia are present.

DAFFINEE, Melrose, Mass.

EFFECT OF THYROID HORMONE AND IODINE ON THE CAROTENOIDS OF THE BLOOD. PIO LUCIANI, Riv. di clin. pediat. **44**:756 (Dec.) 1946.

Among 20 children, several treated with thyroid by mouth, others with iodine and potassium iodide by mouth or subcutaneously, the author noticed some modifications in the carotenoid content of the blood, which seemed to be in relation to the intensity of treatment.

FROM THE AUTHOR'S ABSTRACT.

Hygiene; Growth and Nutrition; Public Health

INFLUENCE OF THE WAR ON VITAL STATISTICS IN THE COMMUNITY OF SIENNA. G. CARDINI, Lattante **18**:257 (May) 1947.

In the province of Sienna, Italy, with approximately 270,000 population, the number of births in the five years preceding the war varied from 4,242 to 4,770 per year and in the five years of the war from 3,351 to 3,775. The number of deaths was about the same each year over the entire ten years, with the exception of 1944, when there was an increase from an average of 3,500 to 5,533. The death rate exceeded the birth rate in each of the war years. The increase in the death rate in children in 1944 is accounted for by bombing casualties and digestive and nutritional disorders. Deaths from other causes, as immaturity, tuberculosis and infectious diseases, did not increase in the war years among children; deaths from respiratory diseases decreased 33 per cent in this period.

HIGGINS, Boston.

MORTALITY IN THE FIRST TWO YEARS OF LIFE IN THE COMMUNITY OF FERMO AND IN AN ORPHANAGE, 1938 TO 1940 AND 1944 TO 1946. M. SANTORO, Pediat. d. med. pract. **22**:16 (Jan.) 1947.

The orphanage at Fermo, Italy, with approximately 200 births yearly, mostly illegitimate, had an increase in the death rate in the two year period 1944 to 1946 over that of the period 1938 to 1940 of from 10.9 to 14.3 per cent. In the community of Fermo, the death rate similarly rose from 8.7 to 12.1 per cent. Although the population increased from 25,438 to 27,123, the number of births diminished from 1,127 to 902. While about 37 per cent of the deaths among children under

2 years of age in the community continued to be due to respiratory infections, the percentage of deaths in the orphanage from this cause diminished from 28 to 3 per cent. Syphilis was responsible for 31 per cent of the deaths among the illegitimate children of the orphanage but for practically no deaths in the legitimately born group in the community.

HIGGINS, Boston.

Prematurity and Congenital Deformities

THE "OPEN" ENDOTRACHEAL METHOD OF ANAESTHESIA FOR HARELIP AND CLEFT-PALATE OPERATIONS IN INFANTS. BLUMY SEGAL, South African M. J. **21**:484 (July 12) 1947.

Segal describes the use of endotracheal anesthesia in infants, with the use of a T tube connected to the endotracheal catheter. By this means, the patient breathes fresh air, together with oxygen and ether. There is no resistance to respiration and no strain on heart or lungs; anoxemia does not occur. The author expresses the opinion that prolonged anesthesia can be employed without untoward results from the anesthetic *per se*.

McGUIGAN, Evanston, Ill.

THE PREMATURE BABY. V. MARY CROSSE, Paediat. danub. **1**:9 (March) 1947.

Mortality due to prematurity will be reduced only by improved social conditions, good antenatal care for all expectant mothers, special care of the infant during premature labor and special care of the premature infant after delivery.

In the case of the larger infants (of more than 4½ pounds [2,041 Gm.] at birth), good results can be obtained in their own homes if breast feeding is achieved, a good nursing technic used and special precautions taken to prevent infection.

Small babies liable to cyanotic attacks, feeding difficulties and other complications of extreme prematurity do best when removed to an institution especially equipped to deal with such infants.

FROM THE AUTHOR'S ABSTRACT.

Newborn

MEASURES FOR THE PROTECTION OF NEWBORN INFANTS: I. DESCRIPTION OF MEASURES INSTITUTED IN MAY 1937 AT LONG ISLAND COLLEGE HOSPITAL; II. PRACTICAL EXPERIENCES WITH PROPHYLAXIS OF DIARRHEA: MANAGEMENT OF A DIARRHEA EPIDEMIC. CHARLES A. WEYMULLER, ALFRED C. BECK and ELIZABETH J. ITTNER, J. A. M. A. **133**:78 (Jan. 11) 1947.

The setup for care of newborn infants in the Long Island College Hospital, New York, includes small nursery units holding 16 babies each. Each unit has all facilities for care of the babies in the unit and is staffed by its own nursing personnel. A common formula room is so constructed and managed that it can serve all the units.

During an epidemic of diarrhea it was proved that a common formula room may serve all hospitalized infants, sick and well, if such a room is properly set up and managed. It was also proved that a clean nursery may be set up and operated immediately adjacent to a unit contaminated with diarrhea, provided the technic described is carefully carried out.

BAIRD, Wauwatosa, Wis.

PENICILLIN IN THE TREATMENT OF NEONATAL SEPSIS. F. M. B. ALLEN, J. EDGAR MORISON and W. R. RUTHERFORD, Arch. Dis. Childhood **21**:19 (March) 1946.

A diagnosis of neonatal sepsis was made in 71 infants, and each alternate infant was treated with both penicillin and sulfadiazine. The remaining babies received sulfadiazine alone and served as controls. A study of the 61 cases which were suitable for analysis failed to show that penicillin increased the recovery rate or influenced either the duration of the illness or the severity of the decline in body weight. The importance in this connection of bacterial infection, especially of the respiratory tract by a potentially variable flora, is discussed. A few infants, chiefly those with staphylococcic infection, were thought to benefit in a further group of 18 treated without controls.

KELLY, Milwaukee.

OTITIS MEDIA IN THE NEWBORN. BARON and PLANSON, Arch. franç. de pédiat. **30**:324, 1946.

This report covers observations made at the Maternity Hospital of Dijon, France, from Dec. 1, 1945 to March 1, 1946. Only the use of the otoscope could have revealed certain of these cases, and the collaboration of the pediatrician and the obstetrician was thus necessary. Among 235 newborn infants there were 23 with otitis. The symptoms were not characteristic, and diagnosis was made usually on the appearance of the tympanic membrane. Paracentesis was practiced uniformly, and penicillin was used without effect. Of the 23 babies with otitis, 7 died; babies at the breast fared much better than those artificially fed.

AMESSE, Denver.

HISTOLOGIC ASPECTS OF A LATE SEQUELA OF KERNICTERUS. LUDO VAN BOGAERT, Ann. pædiat. **168**:57 (Feb.) 1947.

A phase of opisthotonos and violent movements of hyperextension, as well as a suggestion of rotation of the head as sequelae of icterus gravis (erythroblastosis fetalis), follows choreoathetosis with hyperkinesis of facial, lingual and masticating muscles. Thus, the syndrome of the sequelae of icterus gravis is not rigidly fixed.

Anatomically, atrophy of the corpus of Luys and, to a minor degree, of the corpus pallidum corresponds to the neurologic changes. This atrophy is not confined to either of these two nuclei and is liable to evolution. Compared with the other two nuclei the putamen is affected to a slight degree only. All other structures remain unchanged.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

LARYNGEAL DIPHTHERIA AND OTHER INFECTIONS. I. HILMI ALANTAR, Paediat. danub. **1**:149 (March) 1947.

Diphtheria occurs usually after some catarrhal condition. This sequence can be compared with secondary pneumonia of infants appearing as an allergic phenomenon after febrile diseases of the upper respiratory tract. Similar to pneumonia, diphtheria develops in patients who have become susceptible through previous specific or nonspecific diseases, so that the bacilli become pathogenic. Diphtheria is, therefore, not a primary disease but a consequence of other infections.

If the previous infection is not a specific one, as, for example, a common cold, its symptoms are easily mistaken for the beginning of diphtheria. If, however,

it is of a specific nature, it will be at once apparent that the diphtheria is only a secondary development.

Most cases of this condition occur during the winter, especially after epidemics of diseases involving the upper respiratory tract, like influenza, measles and whooping cough. In addition, the primary infection may have exerted a weakening effect on the whole organism and lowered the resistance. The more the resistance is lowered, the easier diphtheria develops and the oftener relapses can be observed. The area involved in the first infection also plays an important part.

FROM THE AUTHOR'S ABSTRACT.

MEASLES IN A KINDERGARTEN. C. PAPP, Paediat. danub. **1**:157 (March) 1947.

Data on an epidemic of measles in a kindergarten was recorded precisely and investigated in every detail. From the results, 2 certain and 4 probable cases prove that immunity developing after a first attack is not permanent. There was an outbreak of epidemic conjunctivitis parallel with the epidemic of measles, the nature and importance of which could not be completely determined.

FROM THE AUTHOR'S ABSTRACT.

EFFECT OF NICOTINIC ACID ON VACCINATION. J. SURÁNYI, Paediat. danub. **2**:3 (July) 1947.

Ninety-six infants were given daily oral doses of 0 to 10 Gm. of nicotinic acid from the day of their vaccination against smallpox. In the vast majority of the treated children, allergic reactions, i. e., areolas and infiltration, were either weak or totally absent. The vesicle itself was as well developed as, or even of a greater diameter than, in the controls. The treatment seemed to affect favorably concomitant symptoms of vaccination, such as pyrexia, itching and tenderness. The degree of immunity developing after vaccination is, however, not yet determined in the treated children.

The results obtained support the theory of the antiallergic effect of nicotinic acid advanced by the author.

FROM THE AUTHOR'S ABSTRACT.

Acute Infectious Diseases

THE ELECTROCARDIOGRAM IN THE DIAGNOSIS AND MANAGEMENT OF RHEUMATIC FEVER. MAURICE SOKOLOW, California Med. **66**:221 (April) 1947.

The electrocardiogram is of major value in the diagnosis of rheumatic fever, in the determination of the presence of a polycyclic course and in the detection of subclinical recrudescences when the patient is allowed out of bed. The electrocardiographic abnormalities represent the commonest manifestation of carditis in adult rheumatic fever and enable one to identify obscure arthralgia or other poststreptococcic illness as rheumatic fever. These manifestations, in 95 per cent of the cases, are partial heart block and significant changes in T wave. The recent work of Rantz and his associates and of Watson and his associates has shown that following respiratory infections with hemolytic streptococci some patients have the classic type of rheumatic fever. Others, however, have minimal or atypical manifestations of illness which were shown to be associated with electrocardiographic abnormalities indistinguishable from rheumatic fever. In clinical practice

one sees such atypical cases, and frequent electrocardiograms are of inestimable value in determining the true significance of the clinical manifestations.

PRYOR, Redwood City, Calif.

A CASE OF OTOGENOUS TETANUS. IVAN MAGAREY, Clin. Rep. Adelaide Children's Hosp. **1**:39 (May) 1947.

Magarey reports a case of tetanus associated with a discharge from the left ear which contained tetanus bacilli. He states that the comparative mildness of the disease was due to the fact that the tetanus infection was implanted in an already chronically diseased ear.

McGUIGAN, Evanston, Ill.

BONE MARROW IN VISCERAL LEISHMANIASIS IN CHILDREN. T. AVERSA and A. CROSCA, Pediatria **55**:207 (April-June) 1947.

Bone marrow studies in 19 children with visceral leishmaniasis revealed four different types of reaction due to the disease. In 9 children, there were erythroblastic hyperplasia, inhibition of cellular evolution and a tendency toward excessive hemolysis. In 7 children, there were erythroblastic hyperplasia, normal or rapid evolution of the cells and a tendency toward excessive hemolysis. In 1 child, there was no erythroblastic hyperplasia or normal cellular evolution, but the tendency toward excessive hemolysis was present. In 2 children, there were erythroblastic hyperplasia, retarded cellular evolution and lack of the tendency toward excessive hemolysis.

HIGGINS, Boston.

ADRENAL CORTICAL HYPOFUNCTION (ADDISON'S DISEASE) IN CHRONIC MALARIA. BAHTIYAR DEMIRAĞ, Ann. pædiat. **169**:65 (July) 1947.

A case of adrenal cortical hypofunction (Addison's disease) in a boy 13 years of age is described. The clinical course and the results of tests proved the absence of adrenal cortical function. A combination of adrenal cortex extract, sodium chloride and vitamins met with good therapeutic success. It is assumed that in this case the cause was chronic malaria, especially since the function of other endocrine glands was also disturbed (hypogenitalism, degeneration of testes) and the connection of such disturbances with chronic malaria has been established by Eckstein. Malignant tumors and tuberculosis of the adrenal gland were not the cause in this special case of adrenal cortical hypofunction.

FROM THE AUTHOR'S ABSTRACT.

Chronic Infectious Diseases

THE VALUE OF THE JUVENILE MANTOUX REACTOR IN THE DISCOVERY OF UNSUSPECTED ADULT TUBERCULOSIS. M. E. CHINNER, Clin. Rep. Adelaide Children's Hosp. **1**:41 (May) 1947.

Routine tuberculin tests are done on all patients at the Adelaide Children's Hospital, North Adelaide, Australia. Investigation of 401 contacts of 128 positive reactors resulted in the discovery of 14 cases of unsuspected adult tuberculosis. The investigation also uncovered many infected cows and thus helped to lessen the chance of the spread of bovine tuberculosis. The results showed that the younger the child with a positive Mantoux reaction, the more certainly was the source of the infection traced.

McGUIGAN, Evanston, Ill.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN: REPORT OF TWO CASES. F. ORLANDINI and TERESA PERI, Lattante **18**:294 (May) 1947.

Two children with tuberculous meningitis had typical clinical histories, family histories positive for tuberculosis and spinal fluids showing positive reactions to Pandy tests and increased cell count and protein contents, but no tubercle bacilli. The children were cured following streptomycin injections. Some reaction, of allergic nature in the authors' opinion, followed injections into the spinal canal; after a period of rest, further injections were given without injury to the child. It is stressed that both intramuscular and intrathecal administration is necessary.

HIGGINS, Boston.

CERVICAL ADENITIS IN INFANTS VACCINATED AT BIRTH WITH BCG. SMILYA A. KOSTITCH-YOKSITCH, Arch. franç. de pédiat. **3**:526, 1946.

The author began observations on cervical adenitis in 1928. Sufficient data have been accumulated through the following eighteen years to establish a proper conception of the pathogenesis. Following a preliminary report of 7 cases in 1931, she now reviews the histories of 70 others showing early involvement of the cervical lymph glands following oral vaccination with BCG at birth.

The clinical evolution of these complications is carefully documented and the extensive contribution is well illustrated. Differential diagnosis from simple adenitis and from tuberculous and syphilitic invasions is given major attention.

The following conclusions are offered: In a certain number of newborn infants vaccinated orally with BCG, one may expect to find, between the second and the tenth month of life, definite cervical adenitis. The penetration of the bacilli occurs through the buccal mucosa. The involvement is of a benign character and the glands subside usually without residuums. The association of BCG with streptococci or staphylococci increases the tendency to suppuration. The inflammation tends to resolve under appropriate treatment with roentgen rays, vitamin D or 10 per cent potassium iodide ointment. When suppuration appears, evacuation should be done early to avoid fistulas and scarring. When BCG vaccination is performed by the oral route, ample quantities of tea should be given immediately to prevent absorption.

AMESSE, Denver.

Diseases of Blood, Heart and Blood Vessels and Spleen

LEUKAEMIA IN CHILDREN: THE EFFECT OF INTRAVENOUS SERUM THERAPY. F. DRAPER, Clin. Rep. Adelaide Children's Hosp. **1**:21 (May) 1947.

Draper discusses results obtained in 3 cases of leukemia by transfusions with pooled human serum. A complete remission lasting six weeks was obtained in 1 case, the bone marrow returning to normal for that time. In another case, the decrease in leukocyte count was comparable to the results obtained by roentgen therapy. He discusses the hypothesis on which his treatment was based, that leukemia could be caused by the production of antibodies which react with living leukocytes. If this assumption be true, he expressed his belief that the release of antibodies from the cells which produce them could be prevented by transfusions of large amounts of serum.

MCGUIGAN, Evanston, Ill.

TWO CASES OF METHEMOGLOBINEMIA IN INFANTS. M. FERRANT, Acta pædiat. belg. **1**:17, 1946-1947.

The cases of 2 infants (4 and 5 weeks of age) are described. Both were fed powdered milk put into solution with well water. The symptoms were severe

cyanosis and anoxia. Methemoglobinemia was the diagnosis, and the analysis of the water revealed a high nitrate content. One child died; the other recovered. Citrated blood and methylene blue were given intravenously.

After explaining the chemical aspects of methemoglobin, the author classifies methemoglobinemias in two groups, methemoglobin in plasma, which is usually connected with conditions causing jaundice and methemoglobin in red blood cells, which may be of intestinal origin (no external cause can be found), of the congenital-familial form or of toxic origin (sulfonamide drugs, aniline, nitrobenzene, nitrites, bismuth and subnitrate). A review of cases reported in the literature and their analyses follow. The author concludes that nitrate is the main cause of methemoglobinemia. Normally, nitrates are produced in the process of digestion and reduced to nitrites and ammonium. These products are not absorbed but, if the mucosa is ulcerated or large quantities are ingested, especially in infants with rapid water metabolism, they may appear in the blood. Methylene blue stimulates the oxygen combustion twenty to thirty times. It is an antidote for hydrocyanic acid; the dose is 1 to 2 mg. per kilogram of body weight intravenously. Biochemically, its action cannot be satisfactorily explained, inasmuch as methylene blue forms methemoglobin itself, but the good clinical experience seems convincing enough to use it as a therapeutic agent. The suggestion was made to use thionine, which is less toxic and more active.

The diagnosis is based on digestive disturbances, cyanosis, anoxemia with dyspnea, shock, tachycardia, red-brown color of the blood, increased number of white blood cells and methemoglobin in red blood cells, with elevation of nitrite in blood.

GLASER, Chicago.

COLD AGGLUTININS IN NORMAL CHILDREN. R. FIANDACA and G. CASCIO, Pediatria **55**:266 (April-June) 1947.

Samples of blood from 100 healthy children between the ages of 3 months and 14 years were tested for cold agglutinins by the method described by Horstmann and Tatlock ("Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia," *J. A. M. A.* **122**:369 [June 5] 1943). Washed red blood cells of group O were found to be agglutinated at 5 C. by a 1:16 dilution of the blood serum after a period of twelve hours in 89 of the 100 children; in 2 children the agglutination was obtained in a 1:128 dilution. These observations suggest the probable cause of death from cold.

HIGGINS, Boston.

CHANCES FOR RECOVERY FROM A FORM OF INFANTILE PERNICIOUS ANEMIA. G. R. BURGIO, Pediatria **55**:277 (April-June) 1947.

Two children, one 12 months and the other 20 months of age, presented in 1938 the clinical and hematologic picture of pernicious anemia. The first child, a girl, showed recovery in a short while under yeast therapy, while the second, a boy, was relieved by liver injections given over a period of one week. Both these children were seen again in 1946; both appeared well and showed no signs of blood dyscrasia; the liver and spleen were not enlarged. This type of megaloblastic anemia of children should not be classified with true Biermer's pernicious anemia, which is characterized by relapses and rarely by complete recovery.

HIGGINS, Boston.

Diseases of Lungs, Pleura and Mediastinum

TREATMENT WITH MASSIVE DOSES OF SULFAMIDOTHIAZOLE IN PNEUMONIA, BRONCHOPNEUMONIA AND BRONCHITIS IN CHILDREN. ROBERTO GIUNTINI, Riv. clin. pediat. **44**:595 (Oct.) 1946.

A total of 50 children of various ages, with pneumonia, bronchopneumonia and bronchitis were treated with one massive dose of sulfamidothiazole, a sulfathiazole derivative, orally, parenterally and intramuscularly administered.

As a control, another group of children of the same age and with the same diseases were treated with the usual system of repeated doses of a sulfapyridine derivative.

The first method showed a therapeutic value equal, if not superior, to the second and usual method, and with the great advantage of simplifying the administration of the drug, greater economy and less frequent symptoms of intolerance.

These advantages suggest that the method of the massive dose may be applied on a large scale in the aforementioned diseases, not only in the children's hospitals, but also at the patients' homes. FROM THE AUTHOR'S SUMMARY.

FOREIGN BODY REMOVED FROM THE BRONCHUS AFTER FOUR MONTHS. E. GYÖRGY, Paediat. danub. **1**:81 (Feb.) 1947.

This 6 year old boy had inhaled an open vial four months before being seen by the author. On bronchoscopy it was observed that the mouth of the vial was open and directed upward into the left bronchus. But the vial could not be removed because of bleeding. Later, after tracheotomy, a deeper bronchoscopy was done, and, on the second attempt with an apparatus devised to place an inflated bulb within the vial, the foreign body was removed.

Bronchopneumonia had existed and was treated with penicillin.

Four months after the operation, the roentgenogram showed diffuse bronchiolectases in the upper lobe of the left lung. GRULEE, Evanston, Ill.

MEDIASTINAL PLEURISY. S. ENGEL, Paediat. danub. **1**:323 (June) 1947.

Mediastinal pleurisy is characterized by a roentgenographic appearance of a triangular shadow projecting to the right in the upper mediastinum similar to the shadow seen in thymic hypertrophy, but extending into the interlobar fissure.

Superior anterior mediastinal pleurisy, although usually occurring in the absence of any preceding pulmonary disease, may follow pneumonia. The condition occurs only in infants and young children and is much commoner on the right side than on the left. GRULEE, Evanston, Ill.

EPIDEMIC OF VIRUS PNEUMONIA IN CHILDREN. BENGT JONSSON, Ann. pædiat. **168**:85 (Feb.) 1947.

Thirteen children were treated in Norrtull's Children's Hospital, Stockholm, Sweden, for virus pneumonia within a short time, and 13 other children with the disease were examined in the outpatient department. The illness took an epidemic course. Positive reactions to the cold agglutination test could be observed. The author discusses the differential diagnosis, especially from pulmonary tuberculosis. Some epidemiologic aspects are mentioned. FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PSYCHOANALYTIC STUDY OF ULCERATIVE COLITIS IN CHILDREN. MELITTA SPERLING, Psychoanalyt. Quart. **15**:302 (July) 1946.

Two cases of severe ulcerative colitis of long standing are described in detail. The onset of symptoms occurred in early childhood, and there was no response to any form of medical therapy. The psychodynamic factors responsible were uncovered through psychoanalytic study of the children. Cures were effected only after prolonged and intensive psychotherapy. Recurrences followed emotionally traumatic experiences and interruptions of the psychotherapy.

In these 2 cases and in similar ones, the author observed that the mother subjected the child to very early and deep frustrations. All these rejecting mothers unconsciously wished to rid themselves of their children. To such mothers, the children reacted with hostile attachment and intense need for the infantile gratification which had been denied them.

Hospitalization is for these children a traumatic experience. The colitis increased during hospitalization and improved on the return home. Ulceration occurred secondarily to the initial inflammation.

Psychotherapy in these cases is extremely difficult and has to include the mother. The author concludes that "prophylaxis would be the best treatment." Prevention of this disease (and of the lesser forms of diarrhea and encopresis so frequently encountered in pediatric practice) could be achieved if the dynamics of their causation were better understood by the pediatrician.

This paper is an extremely valuable contribution to the understanding of a common symptom in childhood. It is impossible in an abstract to do justice to this excellent study or to convey the complex psychosomatic relationships developed therein. Careful study of this paper and the appended bibliography will fully reward any one interested in the subject.

WEINFELD, Highland Park, Ill.

THE INCIDENCE OF CONGENITAL PYLORIC STENOSIS. GEORGE DAVISON, Arch. Dis. Childhood **21**:113 (June) 1946.

Arguments are given for considering the incidence of congenital pyloric stenosis in the United Kingdom to be in the order of 3 per thousand live births. This figure is not significantly different from that given by Wallgren for Sweden.

KELLY, Milwaukee.

PYOCOLPOS IN INFANCY. IAN P. TODD, Arch. Dis. Childhood **21**:118 (June) 1946.

A case of pyocolpos in infancy is recorded. The symptoms and signs of the condition and its treatment are given. Stress is laid on the importance or recognition of the clinical condition and on the simplicity and adequacy of the treatment.

KELLY, Milwaukee.

FAT DIGESTION AND GASTRIC EVACUATION. PETER VÉGHELYI, Ann. pædiat. **168**:93 (Feb.) 1947.

Investigations were made to find out whether retardation of the evacuation of the stomach was a genuine, independent illness or a partial symptom and to determine its immediate cause. Twenty-five healthy children were examined as controls, together with 26 children with acute ailments and 51 with reduced gastric motility. Their gastric juices were examined for the power to split fats and proteins.

The following results were obtained: 1. Active lipase is constantly present in the stomach. It increases with age but the amount is not dependent on the fat content of the food, while the amount of pepsin invariably is. 2. In certain acute illnesses, the lipase is reduced and the evacuation retarded without apparent muscular hypotonia, both returning to normal on restoration of health. 3. In most cases of arterial hypotension, the disturbance of evacuation is accompanied with a reduced rate of fat splitting. 4. The so-called genuine disturbance in evacuation is only a concomitant symptom and dependent on insufficient digestion of fat in the stomach. This is probably due to a weakness of esterase formation which may be a sequel of a recently passed illness.

Treatment should consist simply in a reduction of fat intake.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

THE TRANSFER OF PENICILLIN INTO THE CEREBROSPINAL FLUID FOLLOWING PARENTERAL ADMINISTRATION. WALSH MCDERMOTT and RUSSELL A. NELSON, Am. J. Syph., Gonor. & Ven. Dis. **29**:403 (July) 1944.

McDermott and Nelson studied the effect of transfer of penicillin into the cerebrospinal fluid of 70 patients with late latent syphilis and other infections of the central nervous system. The tests for activity of penicillin in the cerebrospinal fluid were made by four different technics of bioassay.

With the dilution technics of bioassay, no penicillin was demonstrable in the specimens of cerebrospinal fluid obtained from 70 patients who had received penicillin in various dosages by parenteral routes. The presence of neurosyphilis and, in 1 instance, of tuberculous meningitis did not alter these results.

Approximately 0.02 unit of penicillin was demonstrable in the cerebrospinal fluid of patients who had received one or two intramuscular injections of 300,000 to 500,000 units of penicillin three to four hours previously.

In concentrations ranging from 0.078 to 1.25 unit of penicillin per cubic centimeter of serum, penicillin is diffusible through artificial membranes in vitro and into ascitic fluid in vivo. Thus, the failure of the penicillin to appear in the cerebrospinal fluid is not because it is bound to a high degree to nondiffusible elements in the serum.

As a result of their studies, the authors suggest that, since the immediate results of the intramuscular treatment of syphilitic meningitis and other forms of neurosyphilis with penicillin are so promising, it is unnecessary to use the intrathecal route for the treatment of these conditions. In the treatment of purulent meningitis, on the other hand, the administration of penicillin by the intrathecal route cannot be abandoned. GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

THE BRAIN IN INFANTILE CEREBRAL PALSY. HERMAN JOSEPHY, Illinois M. J. **91**:128 (March) 1947.

A variety of pathologic and etiologic factors are connected with the neurologic syndrome of infantile cerebral palsy. The material presented in this paper was obtained from autopsies during a four year period at the Lincoln State School and Colony, Lincoln, Ill. Of 156 patients examined post mortem, 27 were classified as having infantile cerebral palsy. Twenty-two had the bilateral type and 5 the unilateral. All the patients were spastic. This material was observed in an institution for the feebleminded where persons with paraplegia and tetraplegia predominate. These patients exhibited besides the palsy, epilepsy and mental retardation.

The pathologic changes in the seriously affected and the less affected patients were basically identical.

The pathologic lesions of the brain in diplegic and tetraplegic persons are more diversified than those of the hemiplegic group. Malformations of the brain are almost always bilateral and symmetric. Destructive processes, as contrasted to malformations, are found in persons with bilateral palsies, as well as in hemiplegic patients. They are the only lesions occurring in the hemiplegic forms.

Five of the 22 brains taken from patients with diplegia or tetraplegia were malformed. Eleven of them had gross destructions and in 5 no satisfactory anatomic basis was found for the palsy. Four of the 5 patients with hemiplegia exhibited destructions; one did not show any satisfactory pathologic change. All the malformed brains were microgyric and small. The cortex was uneven in width. Usually, both hemispheres were equally affected. None of the malformed brains had any trace of a destructive or inflammatory process.

The second group of brains showed an entirely different pathologic pattern. They exhibited scars as residues of destructive processes. Scar formation was even more complicated in a child's brain than in that of an adult. The conditions exhibited were basically identical, although the gross appearance might be different. The nervous parenchyma was replaced by proliferating glia and mesenchyma.

There are many etiologic factors leading to scar formation in the brains of children with infantile palsy. The chief ones are infections, toxins and trauma. The infections may be antenatal or postnatal. Anoxemia and severe icterus of the newborn are among the toxic factors. Trauma practically always is due to injury at birth.

BARBOUR, Peoria, Ill.

"RELAPSING" AND "RECURRING" MENINGITIS. MAX J. FOX, Wisconsin M. J. **45:** 965 (Oct.) 1946.

Relapsing meningitis is a repetition of the disease syndrome occurring during the convalescent period of the disease. Presumably, the relapse is dependent on persistent infection which is not necessarily demonstrable by clinical symptomatology or laboratory tests. The author strongly emphasizes the necessity for continuance of therapy until convalescence has been well established and normal activity resumed.

Recurring meningitis is a repetition of the disease syndrome occurring after convalescence and often after the patient has resumed his normal activities. Such a recurrence may result from: (*a*) continued contact with the original source of the infection, (*b*) carriers, (*c*) contact with a different antigen and (*d*) persistent foci within the body.

A case of relapsing pneumococcic meningitis and one of recurring meningococcic meningitis are presented.

FROM THE AUTHOR'S SUMMARY.

INTRACRANIAL HYPOTENSION WITH VENTRICULAR COLLAPSE IN THE COURSE OF LYMPHOCYTIC MENINGITIS OF UNKNOWN ORIGIN. FONTAN, VERGER and DABADIE, Arch. franç. de pédiat. **3:**552, 1946.

Craniocerebral traumatism and neurosurgical intervention sufficiently extensive to provoke sudden ventricular depletion were once considered the sole causes for the syndrome of intracranial hypotension. It has now been demonstrated, however, that this syndrome may be seen in the course of such infections as cerebrospinal meningitis. Nontraumatic cases in early life are not exceptional. Detailed observations of such an invasion are presented, the patient being a girl 4 years of age with a cryptogenetic type of lymphocytic meningitis. Recovery was without sequelae after hospitalization of two months.

AMESSE, Denver.

Psychology and Psychiatry

MONGOLISM. HAROLD CUMMINS and R. V. PLATOU, South. M. J. **19**:925 (Dec.) 1946.

A test is presented which the authors hope will prove to be a reliable confirmation of mongolism. It is based on studies of the skin patterns of the hand. Those markings most consistent in the hands of known mongoloid idiots were: (1) a distinctly transverse alinement of skin ridges in the distal region of the palm; (2) an expansive and discretely rounded pattern of ridges in the hypothenar area, forming a clearly discernible arch, whorl or loop, and (3) a triradiate arrangement of ridges at or near the center of the palm. Inked palm prints provided records for study.

A series of 83 normal and mongoloid children was studied. When these criteria were used, 92 per cent of the diagnoses agreed with the clinical diagnoses.

LOGAN, Rochester, Minn.

NEUROPSYCHOLOGIC ASPECTS OF ONYCHOPHAGY IN CHILDREN. M. SCHACHTER, Arch. franç. de pédiat. **3**:558, 1946.

An intensive investigation of the obnoxious habit of nail biting has been made in the neuroendocrine clinic at Marseille, France. The study concerned 150 cases among abnormal children, but results of a similar survey with normal subjects have not yet been reported. The odd superstitions and the folklore concerning the care and the function of the nails current even today in Switzerland are discussed. The author's observations show that nail biting is seen most frequently among boys and that the habit is apt to be found in families with an unfavorable psychologic and economic background.

AMESSE, Denver.

VARIATION IN INTELLIGENCE QUOTIENT IN TEN MENTALLY DEFICIENT CHILDREN UNDER A PEDAGOGIC PLAN. M. I. JOHNSON and N. M. TAVELLA, Arch. argent. de pediat. **26**:268 (Oct.) 1946.

This is the continuation and conclusion of a paper that began in the September issue.

The authors concluded that the intelligence quotient is an indispensable datum when the intellectual efficiency of a child is to be determined. The more near to 100 the intelligence quotient is, the more it will indicate the possibilities of intellectual efficiency. This is true when the atmosphere for learning and the child's emotional response and behavior are normal.

The intelligence quotient is not an index of the innate mental ability; it represents only intellectual efficiency, which is the final result of a series of processes that depend on the mental aptitudes, the environment and the effectiveness of the child's training. The intelligence scales, as the Binet, give an index of the capacity for learning at the time of their use.

The intelligence quotient is a good index of the degree of retardation, if it is interpreted with consideration of other factors, such as health, environment, economic and social conditions of the parents, opportunities for learning, experiences and schooling, verbal stimuli, practical aptitudes and emotional states.

The tendency to use the intelligence quotient as a means of diagnosing mental deficiency without consideration of the other factors which integrate the mental life and determine intelligent behavior is being given up.

If a child has an intelligence quotient of 85 to 90, it will have difficulties in school.

The variations in the intelligence quotient are always reflections of intellectual efficiency in normal children, as well as in children with mental deficiency. In children with mental deficiency, it is always possible to improve the intelligence quotient, even though it is as low as 35, provided the chronologic age is not over 6 to 7 years.

When the intelligence quotient increases at least 10 points, it is possible to notice important changes in the child's intellectual, emotional and social behavior. This fact describes graphically the close relation of the various factors which determine and condition the different aspects of mental life.

ROJAS, Boston.

SCHIZOPHRENIA IN CHILDHOOD. JOSEF APETAUER and JAN FISHER, Pediat. listy **1**:80, 1946.

A 14½ year old boy, with a slight degree of debility, had schizophrenia from the age of 11½ years. Insulin and electric shock treatment caused only temporary improvement.

FROM THE AUTHORS' SUMMARY.

Diseases of the Genitourinary Tract

A CONDITION RESEMBLING PORPHYRINURIA. J. TAMÁSI, Paediat. danub. **1**:75 (Feb.) 1947.

A child 2 years of age suddenly fell ill with symptoms of influenza and abdominal complaints. The urine he voided was dark reddish brown and changed to a deep black after a few hours' standing in an enameled chamber pot. At first, the rare condition of acute porphyrinuria was suspected to be present. A careful chemical analysis disclosed, however, no traces of porphyrin. The color resulted from the ingredients of germicid,® the drug administered, that is, from oxysulfochinolin and phenyldimethylamidodimethylpyrazoline. The latter is excreted in the form of rubasonic acid. The compounds, coming into contact with the iron sides of the pot through the cracks in the enamel, gave the black reaction characteristic of chinolin.

In order to confirm the hypothesis, germicid® was administered again and the urine collected subsequently in a glass cylinder. Part of the urine was then transferred into the pot and both left standing at room temperature. The color of the urine in the cylinder remained unchanged, while that in the pot became deep black again.

FROM THE AUTHOR'S ABSTRACT.

NOCTURNAL ENURESIS. P. ROBOZ, Paediat. danub. **1**:208 (April) 1947.

It is emphasized that each child with enuresis must be examined quite as thoroughly as one with any other disease. The method of diagnosis is threefold: (*a*) drawing a genealogic tree to obtain information on the extent of the inherited inclination, (*b*) determining the type of condition present and (*c*) making a psychologic examination. The last portion is likely to throw light on the mental causes of enuresis and on the role played by faulty education and to reveal the character type to which the child belongs. These data make it possible to establish the prognosis and to make a plan for treatment, which, however, should be adapted to the individual conditions.

Before beginning the treatment proper, any errors in education have to be eliminated. The parents must be told that enuresis is a disease rather than a type of misbehavior and, therefore, cannot be abolished by corporal or other

punishment. The condition must be prevented from becoming the main center of the child's life. Further advice on these lines depends always on the needs of the individual child. No treatment should be prescribed until the character of the child and the importance of the psychologic causes have been taken into consideration.

The genealogic tree is of much help in establishing the prognosis. In families affected with epilepsy, enuresis is an obstinate condition. I believe that in these cases the influence of hereditary factors manifests itself with an unparalleled intensity. Enuresis may not infrequently occur as an equivalent of epilepsy.

The type of the disease may give useful information concerning the part played by psychologic factors in its origin. It can be assumed that psychologic causes are always responsible for the manifestation of periodic forms, inherited inclination probably being low in such children. They can be treated adequately by any kind of psychotherapy, especially suggestion. In some instances mere educational advice may prove of help. A method suggested by the author follows.

A bitter drug (tincture of amara or valeriana) is prescribed. Attention should be directed to the efficacy of the liquid and the child told expressly to observe accurately the directions—to take 5 drops before going to bed. The results are carefully noted in a diary and examined in a week. This procedure leads, as a rule, to some improvement; the child may not wet his bed for several days, and there are even cases when the condition disappears for good. Whatever the result is, however, the treatment should be continued. When enuresis has ceased, the doses are gradually reduced and after some weeks the drug given up. Follow-up examinations are advisable. In case of only temporary success, the physician should declare that the effect, although evident, was not realized fully, as the doses were too small. Increased doses hardly ever fail to give complete results.

It is not claimed that this is the only method leading to success. Suggestion can be applied by various means. Their success depends entirely on the familiarity of the physician with the factors determining this condition and with the methods of appropriate treatment and the prospects for cure.

FROM THE AUTHOR'S ABSTRACT.

Diseases of the Ductless Glands; Endocrinology

EARLY OCULAR MANIFESTATIONS IN THE LAURENCE-MOON-BIEDL SYNDROME. D. J. LYLE, Am. J. Ophth. **29**:939 (Aug.) 1946.

Lyle reports 2 cases and describes the Laurence-Moon-Biedl syndrome. He notes that resemblance to hereditary optic atrophy (Leber's disease) and the various types of cerebromacular degeneration with central scotoma, loss of vision and cerebral symptoms are remarkable in the early stages of the two conditions. In the later stages the pigmentary degeneration may be confused with typical retinitis (retinosis) pigmentosa by the casual observer who fails to take a detailed history of the case and to make a complete examination in order to reveal the other components of the syndrome.

W. S. REESE. [ARCH. OPHTH.]

THYMOMA. W. G. WYLLIE, Proc. Roy. Soc. Med. **39**:591 (Aug.) 1946.

A thymoma was found and removed in a baby 3 months of age. The child made an uneventful recovery.

WILLIAMSON, New Orleans.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

William Elghammer, M.D., *President*

Regular Meeting, March 16, 1948

Analysis of 259 Living Premature Infants Weighing 735 to 1,260 Gm. at Birth. Dr. Julius H. Hess, Miss Evelyn C. Lundeen, R.N. (by invitation), Dr. Ralph Hess Kunstadter, Dr. Howard A. Engle, Baltimore (by invitation) and Dr. Theodore M. Shapira (by invitation).

Report of the Joint Maternal Welfare Committee of Cook County. Dr. James E. Fitzgerald (by invitation) and Dr. Heyworth N. Sanford.

The formation of standard regulations for all nurseries for the newborn in Chicago was undertaken by the joint committee in 1935. These were put into operation in 1937. There has been a steady decrease in the mortality of the newborn in Chicago since that time. Inasmuch as these regulations were formulated ten years ago, some changes are no doubt necessary. They will be undertaken by the joint committee in the near future. It is also interesting to note that the American Academy of Pediatrics has become interested in this subject and has sent out suggestions for procedures in newborn nurseries. A comparison shows that the procedures suggested by the committee are quite similar to those suggested by the academy.

Two years ago the joint committee formed a subcommittee to study mortality in infants up to 1 year of age in Chicago. This committee was composed of Dr. J. R. Gerstley, Dr. A. H. Parmelee, Dr. G. N. Krost and Dr. H. N. Sanford, with Dr. H. B. Lander, from the Health Department. Dr. Parmelee has since resigned and Dr. Joseph Greengard has replaced him. In the opinion of this committee, at present the situation with regard to premature infants in Chicago is being handled as well as possible and needs no study. Also, in regard to mortality in newborn infants, 90 per cent was discovered to be due to congenital defects and conditions not at present remediable. It was, therefore, decided to confine the committee's activities to the other 10 per cent of newborn infants and to infants above the age of 2 weeks. Dr. Herman N. Bundesen, health commissioner of Chicago, has given the fullest cooperation; all deaths in this category occurring in Chicago during the past year have been studied. It is the present opinion of the committee that a sufficient amount of material has not been collected to make a worth while statistical report, but this will be done at a later date.

Regular Meeting, April 20, 1948

Association of Maternal Polyhydramnios with Congenital Atresia of the Upper Alimentary Tract in the Newborn. Dr. Vernon R. DeYoung.

This report includes 4 cases of congenital atresia and calls attention to reports in the literature of other observers to the effect that maternal polyhydramnios may be a useful diagnostic sign in the syndrome of congenital atresia of the upper part

of the alimentary tract. In each of the 4 cases presented the mother had polyhydramnios. Whenever a newborn infant vomits forcefully immediately after birth, and with the absence of the contents of the amniotic sac from the meconium and the presence of pronounced peristaltic waves in the epigastrium, maternal polyhydramnios may be considered to indicate atresia high in the alimentary tract. Fetal alimentary absorption plays an important part in maintaining proper hydrodynamics in the maternal amniotic sac. A case of congenital stenosis of the duodenum, in which incomplete obstruction of the proximal portion of the intestinal tract spared maternal polyhydramnios, is discussed.

Cardiac Hypertrophy in Infants Due to Origination of the Left Branch of the Coronary Artery from the Pulmonary Artery. DR. BENJAMIN M. GASUL.

Four cases are discussed.

CASE 1.—This infant was first seen in January 1938, because of failure to gain weight, occasional loose stools and severe crying spells, especially during and after feedings. Examination revealed decided cardiac enlargement, no cyanosis and no murmurs. Several electrocardiograms showed what appeared to be a coronary infarct. Later roentgenograms showed a bulge in the region of the left ventricle, which was interpreted as an aneurysmal dilatation. The baby died at the age of 13 months.

CASE 2.—A cough and rapid respirations suddenly developed in this 3 month old baby. Examination revealed prominent cardiac enlargement, no cyanosis and no murmurs. The baby died suddenly, and autopsy showed the left branch of the coronary artery originating from the pulmonary artery. There was pronounced dilatation of the left ventricle, with replacement by fibrous tissue in the regions supplied by the left coronary artery.

CASE 3.—A 2 month old infant became acutely ill with fever, dyspnea and cough. A roentgenogram of the chest revealed pronounced cardiac enlargement, no murmur and no cyanosis. At autopsy the observations were exactly similar to those in case 2.

CASE 4.—This 3 month old infant had periodic attacks of dyspnea and became acutely ill with cough and slight fever. On examination, definite cardiac enlargement was noted, with no murmur and no cyanosis. An electrocardiogram showed a "typical" coronary infarct. At autopsy, the observations duplicated those on the other patients.

Bland, White and Garland reported a similar case in 1933. Although they did not make a clinical diagnosis, they were the first to point out the characteristic pathologic and clinical clues resulting from this malformation. Since that time, several cases have been reported in which clinical diagnosis was made. Before the publication of the article of Bland and his associates, this malformation was considered a rare pathologic curiosity. Now it is both a pathologic and clinical entity, and, if sought for by pathologists and clinicians, it is evidently not so rare as was thought.

These babies all die because the left ventricle receives nonoxygenated blood from the pulmonary artery, under decreased pressure as compared with that in the aorta. One reason the infants live for at least two or three months is the possible patency of the ductus arteriosus for several months.

The question is asked whether it may be possible to connect the aorta and the pulmonary artery just above the origin of these vessels and thus supply oxygenated blood under increased pressure to the left coronary artery.

In conclusion, the clinical picture in congenital malformation of the left branch of the coronary artery originating from the pulmonary artery is summarized. It is characterized by prominent cardiac enlargement, absence of cyanosis and murmurs, roentgenologic findings of enlargement of the left ventricle and electrocardiographic signs of coronary thrombosis.

Observations on Ninety Patients Operated on for Congenital Pulmonary Arteriostenosis. DR. JOHN F. DAMMAN JR. (by invitation).

John L. Reichert, M.D., *President*

Regular Meeting, Nov. 16, 1948

Bronchiogenic Cysts of the Mediastinum. DR. L. MARTIN HARDY.

Eighty-two patients with bronchiogenic cysts have been reported on in the literature; 53 were operated on, with 49 recorded as recovered. All the patients were 18 years of age or older, except one 9 month old infant. The cyst in this infant was not actually within the mediastinum but was attached to it by a pedicle.

A detailed report is given of the case of a 10 month old boy who had a bronchiogenic cyst lying between the esophagus and trachea, attached to the left main bronchus. Roentgenograms with bronchoesophagrams demonstrated the mass. The cyst was successfully removed, with complete recovery of the patient. A photomicrograph of the cyst wall is presented.

Bronchiogenic cysts are generally considered to be congenital structures formed by the pinching off of a small bud or diverticulum of the foregut. They are frequently seen in the posterior mediastinum, usually near the bifurcation of the trachea. They are commonly smooth, ovoid or round, containing a clear, thick, jelly-like fluid. The walls of a bronchiogenic cyst are usually lined with ciliated pseudostratified columnar epithelium and have glands secreting mucus in the submucous tissue and also plaques of cartilage.

The symptoms, if any are produced, result from the location and size of the mass and the pressure produced on the surrounding structures. Bronchoscopy, esophagoscopy, roentgenograms and bronchoesophagrams are of the greatest aid in diagnosis.

Dermoid cysts and teratomas are usually lobulated. Dermoid cysts are frequently in the anterior mediastinum. Neurogenic tumors usually produce erosion of the ribs. Malignant tumors should be suspected when the mass is decreased in size following roentgen ray treatment.

There is a frequent possibility of malignant degeneration in benign mediastinal tumors; therefore, operative removal is advisable.

DISCUSSION

DR. PAUL H. HOLINGER: This is an interesting and unusual case, and it raises the question of differential diagnosis of chronic respiratory obstruction in infants. The presence of a double aortic arch or of other cardiovascular anomalies which lead to a similar picture must be considered. This case also demonstrates the value of exploratory thoracotomy, which may now be done with safety in children

and adults and compares in indications and value with exploratory laparotomy. This is an interesting report and I want to congratulate Dr. Hardy and Dr. Willis F. Potts on the successful management.

Treatment of Leukemia in Children. Dr. Mila Pierce, Evanston, Ill.

A series of 80 cases of leukemia, collected over a ten year period, in children treated by the various agents available for control of the disease and its multiple complications, is reported. Twenty-six children were treated with radioactive phosphorus, 11 with 4-aminopteroylglutamic acid (aminopterin®). Of the 43 cases which antedate the antibiotic era, 32 were of children treated with transfusions only; 3 children were treated with external radiation, and 8 were untreated. This group of 43 patients serves as a control for evaluation of those treated by radioactive phosphorus and 4-aminopteroylglutamic acid.

Of the 26 children treated with radioactive phosphorus, clinical remissions were obtained in 8, or 30.6 per cent. Remissions in the hematologic findings occurred in 4, or 15.4 per cent. No remissions were obtained in 14, or 54 per cent of the patients.

Of the 11 patients treated with 4-aminopteroylglutamic acid, remissions were obtained in 7, or 63 per cent.

In 32 children treated with transfusions alone, the duration of life was shown to be prolonged as compared with that in untreated children. With multiple transfusion therapy, the duration of life in children 1 to 6 years of age was fourteen weeks and in children 7 to 14 years of age, twenty weeks.

With radioactive phosphorus, the average duration of life was further prolonged to twenty weeks in children 1 to 6 years old and to thirty weeks in children 7 to 14 years old.

Under 4-aminopteroylglutamic acid, the duration of life in the small series reported did not exceed that obtained with radioactive phosphorus. Six of these children are living and 5 are dead.

With radioactive phosphorus, the duration of remission varied from three to eight weeks. Repeated remissions were obtained in individual children. The longest duration of life after the onset of treatment was sixty-four weeks. Although satisfactory clinical improvement was obtained, hematologic remissions were not as complete as those obtained with 4-aminopteroylglutamic acid.

Under therapy with this drug the longest duration of remission has been ten weeks. The essential difference in the character of the remissions has been the return to the normal pattern of granulopoiesis and erythropoiesis in the bone marrow, which has been well sustained for more than ten weeks in some instances.

The toxic effects of 4-aminopteroylglutamic acid are reviewed and the probable nature of its effect on leukemic tissue is discussed.

DISCUSSION

Dr. B. J. Grossman: In conjunction with Dr. Pierce's work on patients my colleagues and I have, in our laboratory, studied the effects of 4-aminopteroylglutamic acid on normal animals. It was noted in several of her cases that serious hemorrhagic manifestations occurred during the course of therapy. Farber, from September 1947 to August 1948, had 65 cases of leukemia treated with this drug in which the severest complication was hemorrhage. This occurred usually in the first ten days of the therapy. We felt that if the patient could be carried over this period the results of therapy could be improved. Our experimental study was undertaken to ascertain whether 4-aminopteroylglutamic acid itself would produce

hemorrhage and, if so, whether it could be controlled with toluidine blue. Five dogs were given 0.5 mg. of the pteroylglutamic acid antagonist daily; two dogs were given 1 mg. and 1.5 mg., respectively. The animals were studied for changes in the blood picture, especially changes in the clotting mechanism.

The dog given 1.5 mg. of 4-aminopteroylglutamic acid daily died after three doses of the drug. It did not show any toxic symptoms immediately prior to death but a rapid fall in white count and prothrombin activity was demonstrated. The dogs given 0.5 mg. daily lived for longer periods. There were transient increases in the clotting time; the prothrombin activity was maintained until just before death. The most striking change was in the heparin protamine titration, which was increased, indicating an increase in a circulating heparin-like material.

These dogs showed toxic effects four days prior to death, including diarrhea, vomiting and anorexia; one had hematuria. Those carried for ten days or more showed extensive bleeding, particularly from the gastrointestinal tract and from the margins of the gums. These were treated with toluidine blue, and we observed that bleeding could be completely controlled in six to twelve hours.

When 4-aminopteroylglutamic acid was not given and antiheparin therapy was not used, the bleeding continued for four days and finally stopped spontaneously. The bleeding occurred at times when the heparin protamine titration was increased, and we could not account for the bleeding on the basis of a thrombopenia or on the basis of prothrombin deficiency. We concluded that the drug could cause bleeding and that this bleeding could be controlled by toluidine blue.

On the basis of the results of these experiments it seems advisable to use toluidine blue or protamine sulfate during the first ten days of therapy as a prophylaxis against hemorrhage and to use these antiheparin agents if hemorrhage occurs during the course of therapy.

DR. J. GARROTT ALLEN: Leukemia certainly presents many difficult problems. It comes to the attention of my colleagues and me only in connection with the problem of hemostasis, which is of interest to the surgeon, internist and pediatrician alike.

Hemorrhagic disease may manifest itself in several ways; increased capillary fragility, prolongation of the clotting mechanism and thrombopenia. These disturbances may occur alone or in various combinations, in different circumstances. The factors responsible for prolonging the clotting time are largely limited to the plasma itself. Several of these plasma factors are prothrombin, prothrombin conversion factors, fibrinogen and anticoagulants. We observed a circulating anticoagulant in patients with leukemia and certain other diseases of the blood, which accounts for part of the hemorrhagic picture seen in these states. This anticoagulant is similar to, although not necessarily identical with, heparin. The anticoagulant may at times be an important factor in the bleeding episodes which these leukemia patients are prone to demonstrate. Some of the patients described by Dr. Pierce have had an anticoagulant in their blood. This was demonstrated by the use of the protamine titration. In addition to the heparin-like substance, most of the patients of Dr. Pierce had thrombopenia and evidence of increased capillary fragility. These have responded, in part or completely, to the administration of toluidine blue and/or protamine sulfate. In order to interpret the response obtained through the use of these drugs, a complete knowledge of the known factors relative to hemostasis is essential.

DR. HARRY A. WAISMAN: Dr. Pierce has made a complete summary of this work. My colleagues and I have been interested in the same problem. There are several aspects in which our experiments parallel hers closely, more so in the patients of the younger age group, especially those between the ages of 1 and 5.

The effectiveness of folic acid antagonists has been in the complete reversion of bone marrow to normal. We have had our longest remission of twenty weeks in a 3 year old boy. For some reason not completely explained, the toxic effects are notable primarily in oral lesions; we have seen less toxic effects elsewhere. I think basically lesions were due to the level of the drug we used—1 mg. each day, starting with 0.5 mg. and reducing or increasing the amount according to the response.

The use of 4-amino-*N* methyl-pteroylglutamic acid (A-methopterin®) has occupied our attention. We have used 4-aminopteroylglutamic acid and when we obtained the desired effect we gave A-methopterin.® It is apparently less toxic and the oral lesions are relatively less frequent. The dosage of A-methopterin® is about 5 mg., but we have used as little as 2 mg. daily. The oral lesions are one of the guides we use in dosage in both drugs. These oral lesions are similar to those seen in granulocytopenia, and confirmation of this has been given by others. The lesions on the buccal mucosa we have used as a guide to toxic effects, and we attempt to keep just short of frank oral lesions. The best response in clearing up the lesions is obtained by stopping the drug.

We observed that patients with acute leukemia are able to resist intercurrent infections much better than in previous experience. Infections may be somewhat severer when they do take place and tend to hang on longer. One can only speculate as to the mode of action of these drugs. Certainly it is concerned with the metabolism of white blood cells and of the bone marrow in general.

Action of Intravenous Injections of Histamine on the Blood of Hemophilic Children. Dr. Heyworth N. Sanford; Dr. Stuyvesant Butler (by invitation), and Dr. S. R. Kennedy Jr. (by invitation).

This paper was published in full in the December 1948 issue of the American Journal of Diseases of Children.

DISCUSSION

Dr. Stuyvesant Butler: Not being a pediatrician, I know little about hemophilia, but we are continuing the study of histamine because of certain other features that might be of interest. In the first place, in shock, Dr. M. A. Knisely and his associates showed that there occurs a clumping or sludging of blood in the blood vessels; they state it happens in other serious diseases. In shock there also occurs a disappearance of thrombocytes from the circulating blood. Is the intravascular clumping the result of overwhelming amounts of circulating histamine which cause this breaking up of thrombocytes? To find out, my colleagues and I are studying sludge changes in animals and patients receiving various concentrations of histamine intravenously. We are also studying the physiologic aspects of histamine to ascertain whether it is produced by thrombocytes or removed by thrombocytes.

We wonder whether it would be possible to produce a relatively insoluble pellet of histamine to be implanted under the skin of a person with hemophilia, which would dissolve rather slowly, like the extract of adrenal cortex used in adrenal cortical hypofunction (Addison's disease). At present, we have no test for the histamine levels in the blood. We wonder whether part of the trouble is that the histamine blood level is too low. Perhaps we can determine whether a low production or blood level of histamine may be a primary factor in causing hemophilia.

Book Reviews

Clinical Studies of Besnier's Prurigo (Synonyms: Atopic Dermatitis, Eczema Pruriginosum Allergicum, Neurodermatitis Disseminata) with Special Reference to Its Course, the Significance of Airborne Allergens and the Value of Certain Methods of Treatment. By P. H. Nexmand. Price, 25 kroner. Pp. 236, with 31 illustrations. Copenhagen, Denmark: Rosenkilde & Bagger, Publishers, 1948.

This work constitutes an exhaustive report of clinical investigation done by the author in Denmark on Besnier's prurigo (atopic dermatitis) during more than two years and involving case studies on 100 patients.

After an excellent characterization of the disease and its course, the author passes to a consideration of various factors which appear to influence the course, with special reference to allergy to inhalants which, in his opinion, is one of the most important factors. Cutaneous testing and its significance are well considered. The final sections deal with therapy, and he expresses his feeling that symptomatic local treatment and change of environment are the most effective forms. Generalized use of ultraviolet rays is looked on with favor in treatment of older children, adolescents and adults. Specific desensitization is regarded by the author as being "not generally recommendable for Besnier's prurigo."

From a casuistic point of view this is a most valuable contribution to the literature on pediatric dermatology, although the busy clinician will not find an amount of practical aid in the management of cases commensurate with the length of the work.

Sindroma anémico do kala-azar. By Carlos Trincão. No price given. Pp. 68, with 32 tables. Lisbon, Portugal: Sociedade Industrial de Tipografia, 1948.

From many other studies besides his own, the author concludes that kala-azar is characterized by a diminution of hemoglobin concentration, which in the majority of instances is 30 to 50 per cent. Other important symptoms are a reduction in number of red cells to 2,000,000 to 3,000,000, with a Price-Jones curve of 6.70 to 8.40 microns and a leukopenia of 2,000 to 5,000 cells. Erythroblasts average from 20 to 40 per cent and myelocytes from 11 to 20 per cent. While the thrombocytes are approximately 100,000, the hemorrhagic disturbances so often seen are usually accompanied with granulocytopenia.

There is an extensive bibliography, and, although written in Portuguese, the book is easily understandable to those interested in this subject.

Zieke zuigelingen: Een beknopte handleiding voor de huistarts bij de behandeling van de belangrijkste zuigelingenziekten. By C. H. Verboom. Price, 5.90 gulden. Pp. 212, with no illustrations. Assen, the Netherlands: Van Gorcum & Comp., 1948.

This book is intended principally for the general practitioner. The author discusses most disturbances of the newborn and the diseases of infancy which are of interest to the general physician, stressing therapy insofar as it comes within the range of the practitioner. This book can be of great value, especially when no specialist's help is immediately available.